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June, 1934

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WILLIAM HENRY WELCH

DR. WELCH

April 8, 1850–April 30, 1934

There is no need in this JOURNAL, with which he and all his students and colleagues have so long been closely associated, to set down in detail Dr. Welch's life history and achievements. But in his death on the last day of April of this year we have felt grievously the loss of our great source of wisdom and idealism. It was he who brought to the Johns Hopkins University the stirring enthusiasm that moved Europe at that time in the study of pathology and bacteriology, and it was he who chose the unequalled group of men who under his leadership as the first Dean organised the Medical School and the scientific activities of the hospital.

At first, before the hospital was completed and several years before the Medical School opened, he gathered about him, in 1885, men keen to work in the old laboratory under his direction, and ever afterwards it seems that his most cherished memories hovered about "that little group." He never tired of dwelling on those pleasant days when, fired with his own enthusiasm, those disciples worked at the highest tension and accomplished wonders recorded for the greater part in the first volumes of the Hospital Reports. Councilman was there—indeed, he awaited Dr. Welch on his return from Europe and was his first assistant even before the two-storey laboratory was completed. As pathologist to Bay View he brought material for study long before the Hospital was opened and this was all they had, apart from what they obtained in the course of their many studies of the diseases of domestic animals. Then there were Halsted and Mall and Abbott and Nuttall, and, for a time, Walter Reed and W. T. Howard and Bolton. A little later came Flexner. They were most productive and their work was good. Councilman and Lafleur studied amoebic dysentery; Mall and Halsted the structure of the intestinal wall and intestinal sutures. Reed wrote a brief paper on typhoid necroses.

With Dr. Welch himself the interest in the new bacteriology and the dawn of work on immunity overshadowed everything else and with

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him worked Nuttall, and later Flexner, on the gas bacillus, diphtheria and other things. This was the period of his greatest activity in actual work in the laboratory in Baltimore. When the hospital was opened he performed some autopsies, but after 1893 when the Medical School began its activities, he was forced to leave most of that to his assistants although for some time he was still engaged with work on the gas bacillus.

After that, during his years in the Medical School up to 1917 when he withdrew, he was overwhelmingly occupied with the growth of his ideas on medical education and research throughout the country. He was a prime mover in the organisation of The Rockefeller Institute and until his death was chairman of its board of scientific directors. Universities and great foundations devoted to research or to public health and other humanistic endeavours relied upon his advice. He established the School of Hygiene and Public Health and was its director for years, and after that, the Institute of the History of Medicine over which he presided for some time.

Honors poured in upon him from all sides—not only from institutions in the country but also from the Universities abroad. In the War he was most active and became a Major General. His lectures in Pathology and Bacteriology were fascinating and even now one may read them with the greatest interest, finding a wealth of information and of suggestive thought that is remarkably prophetic of the discoveries of later years. He wrote at length on several subjects, such as thrombosis and embolism, adaptation in pathological processes and immunity; and these essays, which are examples of his extraordinary grasp of the world's literature and thought, form delightful reading and will remain as classics.

Dr. Welch was unique in his phenomenal memory and real comprehension of the enormous expanse of his reading. Nothing of all the detail gathered from the Encyclopaedia, or the Dictionary of National Biography, or the whole of medical literature, seems ever to have faded away, and to the last it was all as clear as ever. And it was not limited to scientific subjects, for he was interested in every sort of human activity and although perhaps he could not remember a tune, he was profoundly informed on the whole history of music, and

could tell you at once who was singing in the Vienna opera in 1850, or that of Dresden in 1873.

His friends were innumerable and he was constantly the generous host at the Maryland and University Clubs. He enjoyed good cigars and good things to eat, and missed none of the famous delicacies of Maryland. A favorite indulgence was in sea bathing, after which he would lie for a long time in the sun on the beach—indeed, he spent the whole of the summer before his illness at the University Club in New York, with daily trips to one of the beaches.

Here he was loved and held in reverence by all of us. He was our standard, our oracle in problems of every sort. His wisdom and his understanding of all sides of any difficult question were recognised and his judicial mind weighed so carefully what was brought before him that all relied on his judgment. Indeed, in whatever we were doing the question ever present in our minds was, "What would Dr. Welch think of this?"

Until the last, throughout his long illness in the hospital, he was alert as ever and interested keenly in the happenings of life around him. It seems a typical example of his bravery that never once, during those fourteen months, did he ask any one about his illness or his prospect for recovery. To have done so would have led to tragic commiseration and this he must have known only too well.

His loss is irreparable, and still we must go on alone. But the memory of his wonderful character, of his lovable personality, of his colossal store of knowledge, and, above all, of his wisdom, will remain with us and encourage us.

W. G. M.

SURGICAL AFFECTIONS OF THE PANCREAS MET WITH IN THE JOHNS HOPKINS HOSPITAL FROM 1889 TO 1932, INCLUDING A REPORT OF A CASE OF AN ADENOMA OF THE ISLANDS OF LANGERHANS, AND A CASE OF PANCREATOLITHIASIS[1]

WILLIAM FRANCIS RIENHOFF, JR. AND DEAN LEWIS

From the Department of Surgery, Johns Hopkins Hospital

Submitted for publication December 14, 1933

In response to an invitation from the Gastro-Intestinal Division of the Southern Medical Association to take part in a symposium on Diseases of the Pancreas, and present the surgical aspect of affections of this organ, we have reviewed the cases of pancreatic disease encountered on the Surgical Service of the Johns Hopkins Hospital from its opening in the year 1889 until the present year, 1932. The present study consists of an analysis of the cases in regard to onset, clinical course, operative treatment, pathological findings and post-operative results.

The etiology of pancreatic diseases, notwithstanding the most interesting contributions, made by numerous and quite ingenious laboratory experiments in the production of pancreatitis, presents problems which are still unexplained. Lesions of the pancreas, excluding neoplasms, seldom occur as primary or isolated conditions, but are usually consequent upon changes in adjacent organs, *i.e.*, in the stomach, duodenum, liver, or the bile passages. The first part of the gastro-intestinal tract is a complex mechanism, made up of a number of organs, which however act physiologically and often pathologically as a unit. This complex mechanism, consisting of the stomach, duodenum, liver and pancreas, may be referred to as the gastro-duodeno-hepatico-pancreatic system. The pancreas, one of the most powerful of the digestive glands, is not the least necessary factor of this group. The important activities of the pancreas: *i.e.*, the exter-

[1] Read before the Gastro-Intestinal Division of the Southern Medical Association at its annual meeting, Birmingham, Alabama, November 15, 1932.

nal and internal secretion of ferments and enzymes, as well as its influence on other members of the endocrine system, might lead one to the conclusion that disturbances of this organ could readily be recognized and diagnosed with accuracy. The reverse, however, is the case. Lesions of the pancreas, excluding neoplasms, are seldom primary and their clinical manifestations are observed mostly because of concomitant diseases or dysfunction of neighboring organs, usually consequent upon changes in the adjacent duodenum, liver, or bile passages. As will be shown, a large percentage of cases of acute as well as of chronic pancreatitis are associated with inflammation of the gall-bladder and biliary calculi. Acute disturbances in the pancreas, rare as they are, simulate closely other abdominal catastrophies, and chronic disturbances are usually overlooked.

In the Johns Hopkins Hospital, from its opening in 1889 until 1932, a period of 43 years, there have been admitted to the Medical and Surgical Services, not including cases of diabetes mellitus, 167 cases of disturbance of the pancreas. It is felt that an analysis of these cases might supply a good index, not only to the incidence of pancreatic diseases in a large surgical service of over 78,000 patients, but also afford a fairly accurate conception of what one may expect to accomplish by surgical measure in the alleviation of disturbances of this gland. Of this group of 167 cases, nine were classified on the Medical Service as instances of pancreatic insufficiency. These nine cases have been excluded from the present study because the patients were not operated upon, and therefore the proof of the existence of any pathological change in the pancreas was lacking. In this study only those cases were included in which the gland was actually proved to be the site of a pathological change (table 1). In the classification of the remaining 158 cases (table 2, chart 1), it was to be noted, that carcinoma formed the largest group, consisting of 109 of the 158 cases, or 68.99 per cent. Far smaller, but second in size, was the group composed of the cases of chronic pancreatitis, which contained 20 cases—12.66 per cent of the total. There were recorded in this period of forty-three years only 18 cases of acute pancreatitis, or 11.39 per cent. That seems a small group indeed, and serves to emphasize the rarity of this condition. Classified under this inflammatory group were 2 cases (1.27 per cent) of pancreatic abscess.

TABLE 1

*Classification of 158 cases of surgical diseases of the pancreas, Johns Hopkins Hospital 1891–1932**

YEAR OF INCIDENCE	CARCINOMA OF PANCREAS	CHRONIC PANCREATITIS	ACUTE PANCREATITIS	PANCREATIC CYST	PANCREATIC ABCESS	PANCREATIC APOPLEXY	ADENOMA OF PANCREAS	TOTAL NUMBER OF CASES
1891	1							1
1892				1				1
1893	1			1				2
1894			1					1
1895	2							2
1896	1							1
1897	1							1
1898								—
1899	1							1
1900								—
1901			1	1				2
1902		1						1
1903	2		2					4
1904	3							3
1905								—
1906	3	3				1		7
1907	1							1
1908	2			1	1			4
1909	3		1					4
1910	3	2						5
1911	1							1
1912	2		2					4
1913	5			1				6
1914	3	2		1				6
1915	4		1					5
1916	1	2						3
1917	6							6
1918	2				1			3
1919	7		1					8
1920	5							5
1921	4	1						5
1922	6		3					9
1923	6	1	1					8
1924	5	1	1					7
1925	2	1		1				4
1926	7	1						8
1927	2	1						3
1928	2							2
1929	6						1	7
1930	2	2	1					5
1931	4	1	2					7
1932	3	1	1					5
Total...	109	20	18	7	2	1	1	158

* Through June 15, 1932.

There were 7 cases, or 4.43 per cent, of pancreatic cysts; one of pancreatic apoplexy, so-called; and one case of adenoma of the gland, which was the only instance of a benign tumor encountered in this

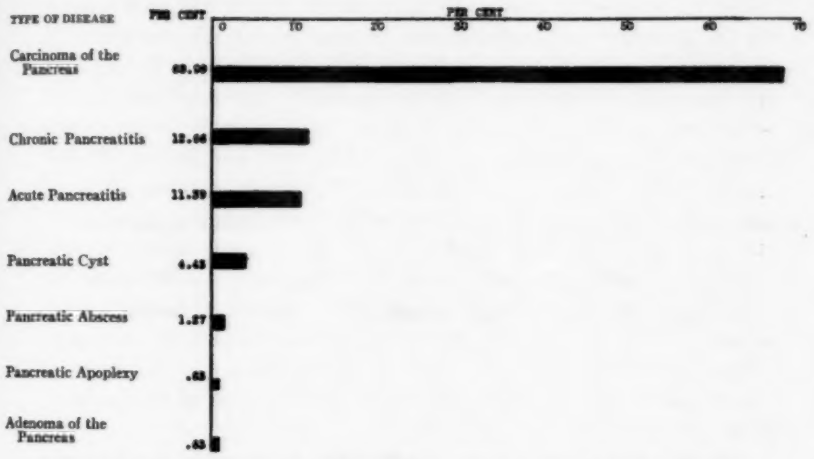

CHART 1. CLASSIFICATION OF 158 CASES OF SURGICAL DISEASES OF THE PANCREAS. JOHNS HOPKINS HOSPITAL, 1891–1932

TABLE 2

Classification of 158 cases of surgical diseases of the pancreas, Johns Hopkins Hospital 1891–1932

TYPE OF DISEASE	NUMBER OF CASES	PER CENT
Carcinoma of pancreas	109	68.99
Chronic pancreatitis	20	12.66
Acute pancreatitis	18	11.39
Pancreatic cyst	7	4.43
Pancreatic abscess	2	1.27
Pancreatic apoplexy	1	0.63
Adenoma of pancreas	1	0.63
Total	158	100.00

series. It is felt that it might be best to discuss these different groups separately, because of the fact that their etiology, pathogenesis, mode of onset, clinical course and treatment all differ in many respects.

ACUTE PANCREATITIS

By far the most interesting condition occurring in the pancreas, from a surgical standpoint, is undoubtedly acute inflammation, or acute necrosis of the pancreatic parenchyma, which has been termed in the literature acute pancreatitis, or acute pancreatic necrosis, and in our present state of knowledge must be considered to be one and the same disease process. It is an unusually rare condition as evidenced by the fact that only 18 cases have occurred in the Johns Hopkins Hospital during a period of 43 years, and in over 78,000 surgical admissions. One of this group of eighteen, who was operated on by Dr. Halsted, (unfortunately too late in the course of the disease, the patient having been stricken on a train en route from Chicago, and dying shortly after admission to the hospital), was autopsied by Opie, who found a gall-stone lodged in the ampulla of Vater in such a manner that regurgitation of bile into the duct of Wirsung occurred. This case stimulated a great deal of speculation as to the cause of acute pancreatitis, and demonstrated certainly one of the possible etiological factors in its production.

There is perhaps no other calamity that can occur in the abdomen as formidable as that of acute pancreatitis. Although a good many statements to the contrary have been made, this clinical syndrome has very characteristic signs and symptoms which make the diagnosis at once fairly clear and it is usually because the surgeon neglects to think of this disease that its presence escapes him. The suddenness of its onset, the extreme agony which accompanies it, and the high mortality so swiftly attendant upon it, combine to render it the most dreadful of abdominal catastrophies. The indescribable pain, very sudden in its onset, and more terrible than that of the perforation of a gastric or duodenal ulcer, comes on often after a good meal. The patient, lying perfectly quiet and flat on his back, presents a marked contrast to the one suffering with hepatic or renal colic who tosses and turns constantly, seeking in vain the desired relief. The painful drawn facies; the history of severe epigastric pain; and the general condition of shock with a thready, imperceptible pulse, associated with cold, clammy, often cyanotic extremities, make up a disease picture that can hardly be mistaken. The history is that of pain

coming on, usually at night, after a full meal. The pain, a most excruciating one, and stabbing in type, is commonly located in the pit of the stomach or epigastrium, but may also be felt in the back and flanks. The patient is in a state of shock or collapse associated with a very rapid pulse which has lost in volume as a result of a fall in blood pressure. The pain is significant because of the fact that it is practically always described by the patient as confined to the epigastrium and back. This backward projection of the pain is rarely, if ever, encountered in gastric or duodenal ulcer with perforation; for posterior perforation of an ulcer is almost more unusual than acute pancreatitis. Also as a rule there is very little elevation of the pulse rate or fluctuation of the blood pressure in cases of perforated ulcer. Thus the contrast between the presence of a state of shock in patients suffering with acute pancreatitis and the absence thereof in cases of perforated ulcer is quite distinct. This state of shock has been attributed by some to the absorption of histamine, formed as a result of the destruction of pancreatic parenchyma by trypsin; by others to the absorption of trypsin itself. The patient thus presents the clinical picture of collapse that could follow a huge hemorrhage, associated with greater agony than that caused by a ruptured viscus. Tenderness and localized rigidity are confined principally to the upper part of the abdomen above the umbilicus, but often remain slight. Even in the early hours a definite fullness may be observed here, the so-called "epigastric peritonitis." This upper fullness and protrusion become more pronounced if the patient survives a few days. It will extend into the lower abdomen coincidently with the development of general peritonitis.

Incessant and early vomiting of clear, and usually greenish-colored gastric juice, due to the admixture of some bile, might create the impression, especially when this symptom alone is considered, of a high intestinal obstruction. This diagnosis, however, can usually be excluded, for the vomitus in these latter conditions soon becomes copious, brownish colored and foul-smelling. In cases of acute pancreatitis it is and remains, as a rule, of pure gastric or duodenal origin.

A peculiar cyanosis of the face and neck, associated with slate-blue patches distributed in the skin over the extremities, to which Halsted had first called attention, is considered almost unknown in acute

abdominal affections other than acute pancreatitis. It is interesting to study the 18 cases of acute pancreatitis which occurred in the Johns Hopkins Hospital and analyze them from the viewpoint of the characteristic signs and symptoms which have in general been attributed to this disease (table 3). In the first and foremost place stands the pain. In each one of the eighteen cases the chief symptom was an agonizing, excruciating, non-migratory pain, which was of the fiercest intensity in the epigastrium, being only occasionally felt in the left and right upper quadrants. The pain was so intense that it produced a state of profound shock. In 16 of the 18 cases, or 88.89 per cent, it was

TABLE 3

Signs and symptoms of patients having acute pancreatitis, Johns Hopkins Hospital, 1891–1932

SIGNS AND SYMPTOMS	NUMBER OF CASES	PER CENT
Pain	18	100.00
Nausea and vomiting	15	83.33
Fat necrosis	12	66.67
Sero-sanguineous exudate	10	55.56
Jaundice	8	44.44
Gall-stones or gall-bladder disease	8	44.44
Loss of weight	4	22.22
Bilirubinuria	4	22.22
Weakness	2	11.11
Constipation	2	11.11
Diminution of pigment in stools	2	11.11
Cyanosis	2	11.11

located principally in the epigastrium and in 2, or 11.11 per cent, in the right and left upper quadrants.

Although jaundice is said to occur quite infrequently in acute pancreatitis, a definite tinting of the sclerae and skin was present in 44.44 per cent of our cases. The jaundice was rather slight but distinct. An attempt was made to determine whether or not the presence of jaundice is an indication of the severity of the intoxication associated with the disease. It was found that of the eighteen patients, eight were jaundiced, and of these three died, a mortality of 37.5 per cent. Of the ten non-jaundiced patients four died, a mortality of 40 per cent. Thus the data obtained from this small

group of cases was indecisive so far as jaundice was concerned, and could not be used as an index of prognosis. Cyanosis was observed in only 2 cases, or 11.11 per cent of the series. One was the case originally described by Halsted and Opie. We were unable to find instances of slate-blue patches in the skin which have been mentioned by others. In 83 per cent of the cases there was a history of early and persistent vomiting. In 8, or 44.44 per cent, gall stones had been removed or the gall-bladder drained for chronic or acute inflammation at a previous operation or there has been found some affection of the biliary tract at the operation for the acute pancreatitis. In the remainder no history of gall-bladder disease could be obtained, nor

TABLE 4

Classification of the white blood count of patients having acute pancreatitis, Johns Hopkins Hospital, 1891–1932

WHITE BLOOD COUNT	NUMBER OF CASES	PER CENT
8,000–11,999	2	14.29
12,000–15,999	3	21.43
16,000–19,999	2	14.29
20,000–23,999	5	35.71
24,000–27,999		
28,000–31,999	1	7.14
32,000–35,999	1	7.14
	14	100.00

was there any information on the hospital histories suggesting it. In 11.11 per cent the stools were clay-colored. In 22.22 per cent the urine showed the presence of bile.

In this series, there was uniformly a leucocytosis (table 4), the white count being elevated from 9,000 to 33,000 with the great majority of the cases running quite high, from 15,000 up to 33,000.

In regard to age distribution, the majority of patients afflicted were between 25 and 50 years of age—15 cases (table 5). There was one case in a patient below twenty-five, and two in patients above fifty-five years.

Although the interpretation of the clinical syndrome of acute pancreatitis may sometimes be confusing and leave one in doubt, the

diagnosis is unmistakable when the abdomen is opened at operation and a blood-stained effusion escapes, or areas of fat necrosis in the parietes or in the omentum are discovered. Fat necrosis is a distinct index of pancreatic disease, and as it occurs when the pancreatic juice finds its way into the neighboring tissues, bears much the same relation to lesions of the pancreas as jaundice does to disease of the liver. Recognition of this lesion and its significance is of the greatest importance to the surgeon. Fat necrosis is the result of the action of the lipolytic fat-splitting enzyme produced by the pancreas, which breaks down the neutral fat into fatty acids and glycerine. The fatty acids

TABLE 5

Age distribution of 49 cases of non-carcinomatous pancreatic diseases, Johns Hopkins Hospital, 1891–1932

AGE	CHRONIC PANCREATITIS		ACUTE PANCREATITIS		PANCREATIC CYST		PANCREATIC ABCESS		ADENOMA OF PANCREAS		PANCREATIC APOPLEXY		ALL NON-CARCINOMATOUS CASES	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
years														
0–14					2	1							2	1
15–24				1				1						2
25–34	1	4	2	2	1							1	4	7
35–44	1	3	1	5	2				1				5	8
45–54	1	3	5					1					6	4
55–64	2	3	1										3	3
65–74	2		1		1								4	
Total...	7	13	10	8	6	1	—	2	1	—	—	1	24	25

then combine with calcium to form an insoluble soap which is deposited as a white precipitate in the sub-peritoneal tissues. As a rule the great majority of these deposits were found, in this group of cases, to be around the pancreas, spreading centrifugally beneath the posterior peritoneum. At times the omentum would be studded with these small white areas which appeared as opaque dots, usually about 1 mm. in diameter. When such deposits are seen in or underlying the peritoneum, there can be no question but that the pancreas is involved. In our series of 18 cases there were 12 in which fat necrosis was said to have been observed. In 5 cases there was no information; in 1 there was no fat necrosis. Of the 12 patients, in whom the fat

necrosis occurred, 6 died and 6 recovered. Fat necrosis, therefore, does not seem to be of any prognostic significance.

The presence of sero-sanguineous exudate would not seem to be quite so constant a feature of the disease or as pathognomonic as fat necrosis. In only 10 cases was there a profuse bloody exudate into the peritoneal cavity; five of these patients died, while five survived. In 8 cases there was no information in regard to the presence or absence of this exudate.

In all cases there was an enlarged, oedematous, boggy infiltration of the pancreas which involved not only the head, but also the body, and even the tail. In the majority of instances the parenchyma was so soft that the fingers could be inserted into the gland by exerting very little pressure, and the parenchyma seemed to be a necrotic mass containing a great deal of old blood and serous exudate. The retro-peritoneal tissues about the pancreas were also infiltrated and oedematous.

Concerning the treatment of acute pancreatitis a number of cases have been recorded in the literature in which it consisted mainly of medicinal measures. All of these patients died. In our present state of knowledge and technical advancement, only surgical interference can rationally be considered, and it has been partially successful. The extent of the surgical procedure and success depends of course in great measure on the general condition of the patient at the time of operation, and the length of time the disease has been in progress. The minimum that should be done in all cases of acute pancreatitis is the opening of the abdomen at the earliest possible moment, a generous exposure and ample drainage, not only of the abdominal cavity as such but down to and within the pancreas itself. This entire region should thereby be walled off and isolated from the remainder of the peritoneal cavity so that a path of least resistance to the exterior may be afforded. Of the 18 such patients who have been admitted to the Johns Hopkins Hospital, all have been submitted to operation. In no case was the disease treated by medicinal measures alone. In fifteen of these drainage was established, not only of the abdominal cavity, but down to and within the pancreas. Of the 15 patients in whom drainage was established, 10 survived and 5 died,—a mortality of 33.33 per cent. In 3 cases in which the abdomen was

closed without drainage one patient survived and two died, a mortality of 66.67 per cent. Although our series is of course small, yet these figures seem to bear out the observations of Moynihan, Whipple, Deaver, Archibald and others, who have in the past made a study of the operative results of the treatment of acute pancreatitis. Unquestionably the rationale of the surgical treatment of acute pancreatitis must be based on the possible etiological factors and over and above the minimal drainage mentioned above, namely, of the abdomen and down through the lesser peritoneal cavity to the pancreas; how much can be accomplished surgically will depend to a great extent on the condition of the patient at the time of operation. Whether or not one may investigate the gall-bladder, the biliary tract, the ampulla of Vater or the pancreatic duct of Wirsung must be left to the judgment of the operating surgeon. For if a stone is firmly lodged in the ampulla of Vater and the patient's condition permits, the removal of this stone would be the method of choice, and certainly the most efficacious surgical procedure. The same reasoning applies to the question of drainage of the gall-bladder and common duct, in this way relieving pressure or infection, or both, from the biliary tract. Such an infection or increased pressure in the bile-ducts causes a regurgitation of bile into the pancreas or an infection through the lymphatics or through the bile-ducts. Follow-up examinations of these patients have been incomplete so far. In the few patients that we have been able to examine it has been found that those from whom stones in the common duct, gall-bladder, or in the pancreas had been removed at the original operation remained free from all symptoms or signs which could have been attributed to their attack of acute pancreatitis. If the patient's condition permits, it would seem well to establish drainage of the gall-bladder and common duct and be certain, if possible, of the patency of the common duct. It might be added, in case the presence of a localized area of induration in the pancreas suggests a stone in the duct of Wirsung, that the latter should be investigated by incision and probing. It would probably be impossible, however, to ascertain the presence of one or more stones by mere palpation of a diffusely enlarged gland, such as is usually encountered in acute pancreatitis. Unquestionably the most important of the surgical procedures in dealing with this condition is *free*

exposure of the pancreas with incision through the posterior peritoneum and capsule of the gland. Drainage down to and into the pancreas should then be established, thus completely walling off the gland, relieving tension, and permitting free access for the escape of pancreatic ferments along the drainage tract. Of 18 patients suffering from acute pancreatitis, 10 or 55.56 per cent were well, 1 or 5.56 per cent improved, and 7 or 38.89 per cent died (chart 2).

PANCREATIC ABSCESSES

Of this type of affection of the pancreas there were only two cases recorded; both patients recovered. When the pancreatitis becomes localized and the focus walled off, the operative treatment is far less

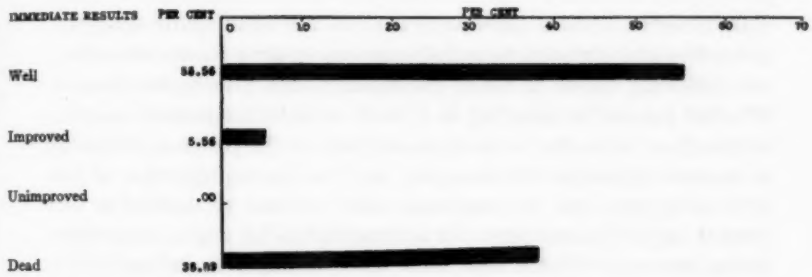

CHART 2. IMMEDIATE RESULTS OF 18 CASES OF ACUTE PANCREATITIS. JOHNS HOPKINS HOSPITAL, 1891–1932

serious and attended by a greatly reduced mortality. Pancreatic abscess is a form of acute pancreatitis in which the virulence of the infecting organisms or the destructive chemical process is less pronounced than in cases of the acute hemorrhagic or necrotic form. Thus, instead of a widespread infection and chemical toxemia, the process becomes localized with the formation of an abscess. It is of course to be realized that between the most virulent and the mild cases there is an unbroken series. As a rule, not only the tumor mass may be palpated in the left upper quadrant, but tenderness also is usually referred to this region. It has been found in our cases and also in others reported in the literature, that the abscesses usually pointed in the region between the spleen and the left lobe of the liver.

It is then quite easy indeed to drain them either anteriorly or through the left flank. It is obvious and need not be emphasized here that an abscess, at first localized in part of the gland, may become diffuse and lead to total destruction of the gland; or it may extend into adjacent or distant tissues and organs. Under such altered conditions the evacuation may require an approach over different routes according to the location in the individual case, and more or less extensive operative measures. Anterior drainage was accomplished in our cases with very successful results. The pus recovered in our cases was sterile. The clinical syndrome of abscess of the pancreas is similar in all respects to acute pancreatitis, but far less fulminating.

PANCREATIC APOPLEXY

In this series of cases there was one of so-called pancreatic apoplexy. It was thought advisable to include this case under a separate heading, but following those of acute pancreatitis and pancreatic abscess. Whether pancreatic apoplexy is a result of an inflammatory reaction in the gland, or is due to an acute necrosis of the pancreas following an extreme chemical irritation as a result of the regurgitation of bile salts or trypsin into the pancreatic ducts cannot be decided in our present state of knowledge. It is nevertheless an acute catastrophe in the pancreas which is associated with autodigestion of the parenchyma, and must be regarded for the present in the same category as pancreatitis. In our single instance an erosion of the superior pancreatico-duodenal artery was demonstrated. It proved to be a fatal calamity in our case as in most of the others reported in the literature. The interesting part about these cases—and probably they are the most fascinating of all the pancreatic affections—is that the change in the pancreas is sudden and at the same time diffuse throughout the entire gland. The extensive necrosis of the parenchyma and even digestion of the large vessels, with profuse hemorrhage into the substance of the gland, probably takes it out of the category of inflammations. The entire course is too fulminating and rapid for an inflammatory reaction that would undoubtedly consume much more time. This fulminating necrosis would seem rather to be the result of a sudden perfusion of the gland with a most energetic digestive substance, such as activated trypsinogen associated possibly with

other ferments of the pancreas. The rapid clinical course, the complete necrosis of the pancreas, terminating in death, are all suggestive of a devastating chemical reaction rather than an inflammatory process.

CHRONIC PANCREATITIS

The clinical manifestations of this disease are also somewhat nebulous and indefinite. The symptoms of chronic pancreatitis are quite similar in many respects to those characteristic of malignant disease of the head of the pancreas; indeed there have been many cases in which an erroneous diagnosis of carcinoma has been made. Our criterion for the presence of this affection of the pancreas, in the great majority of cases in this series, as well as those reported by others, was the impression gained from palpation by the hand of the operating surgeon, as to whether or not the induration of the pancreatic gland was sufficient to remove it from the category of normal. There is, of course, a great deal of room for error in this method. Experience in palpation of the normal, as well as the diseased gland, with full recognition of the departures from normal which may be encountered in the ordinary exploratory operation, unrelated to disturbances of the pancreas, impress one with the necessity for great caution in ascribing changes in the consistence of the gland to pathological processes therein. For there may be wide departures from normal in size and consistence, that fail to reveal any pathological change on microscopic section.

In twenty cases of chronic pancreatitis, all of which were operated upon, the gross and in some instances the microscopic changes in the pancreas were felt to indicate undoubtedly the presence of a chronic inflammation of the gland. As stated in the beginning, from this group were excluded all cases of diabetes mellitus and all cases in which there was the slightest suspicion of neoplastic change in the pancreas. One of the most characteristic symptoms (table 6), which was found to be present in 19 (95 per cent) of the cases, was chronic, deep-seated, boring pain in the epigastrium (table 7), this being of a dull, aching character, non-migratory, from which the patient had great difficulty in obtaining relief. It differed in this respect from the lancinating pains of gall-stone or renal colic, and also in not having the periodicity or being susceptible to alleviation as are the pains of

ulceration of the stomach or duodenum. Nausea and vomiting were present in 90 per cent, while loss of weight was found in 60 per cent of this group of cases. In 35 per cent outspoken jaundice was observed and in 20 per cent additional a peculiar brownish pigmentation of the skin entirely unlike the staining of the skin by the bile pigments was

TABLE 6

Signs and symptoms of patients having chronic pancreatitis, Johns Hopkins Hospital, 1891–1932

SIGNS AND SYMPTOMS	NUMBER OF CASES	PER CENT
Pain	19	95.00
Nausea and vomiting	18	90.00
Loss of weight	12	60.00
Diminution of pigment in stools	8	40.00
Jaundice	7	35.00
Weakness	5	25.00
Pigmentation of skin	4	20.00
Gall-stones and gall-bladder diseases	4	20.00
Constipation	3	15.00
Bilirubinuria	3	15.00
Itching	2	10.00
Blood in stool	1	5.00
Diarrhoea	1	5.00

TABLE 7

Location of pain in cases of chronic pancreatitis, Johns Hopkins Hospital, 1891–1932

LOCATION OF PAIN	NUMBER	PER CENT
Epigastrium	14	73.68
Upper right quadrant	2	10.53
Abdomen	1	5.26
Left side	1	5.26
Right hypochondrium	1	5.26
Total	19	99.99

demonstrated. Itching of the skin was complained of in only 10 per cent and constipation in only 15 per cent. However, in 40 per cent the color of the stools was less pronounced than normal and they were reported as appearing whitish to clay-colored, or putty-like. It was in this latter group that a complication with gall-stones or

diseases of the gall-bladder and ducts was revealed by the past history or through the operation in about 20 per cent of the cases. Azotorrhea or steatorrhea was not present in any of the cases of this series.

TABLE 8

*Deaths from diseases of the pancreas, United States Registration Area, 1921–1929**

YEAR	DEATHS		
	Both sexes	Male	Female
1921	489	254	235
1922	432	203	229
1923	525	258	267
1924	568	299	269
1925	562	265	297
1926	579	277	302
1927	584	282	302
1928	633	290	343
1929	640	325	315
Total.....	5012	2453	2559
Per cent.....	100.00	48.94	51.06

* Mortality Statistics—Department of Commerce, Bureau of the Census, page 76.

TABLE 9

*Estimated yearly population of the United States, 1921–1929**

YEAR	POPULATION
1921	107,417,062
1922	109,123,505
1923	110,829,947
1924	112,536,390
1925	114,242,832
1926	115,949,275
1927	117,655,717
1928	119,362,160
1929	121,068,602

* Based on figures from the Fifteenth Census of United States Population, volume III, part 1, page 14, 1930.

In only one case was blood found in the stool and its origin was not determined. An enlargement of the pancreas in size and an increase in consistence were revealed at operation in all of the cases. In the

majority the pancreas was diffusely enlarged and in a few only the head of the gland was involved, but in all cases the head seemed to be the starting-point for the enlargement and subsequent induration,

TABLE 10

*The annual death-rate per 100,000 from diseases of the pancreas, other than diabetes mellitus and carcinoma, in the Registration Area of the United States, 1921–1929, all classes**

YEAR	DEATH RATE PER 100,000
1921	0.455
1922	0.396
1923	0.474
1924	0.505
1925	0.492
1926	0.499
1927	0.496
1928	0.530
1929	0.529

* Based on figures from Mortality Statistics 1921–1929; and estimated population of United States based on figures from Fifteenth Census United States Population, volume III, part 1, page 14, 1930.

TABLE 11

Result of operations upon persons having chronic pancreatitis, Johns Hopkins Hospital, 1891–1932

TYPE OF OPERATION	RESULTS								TOTAL
	Well		Improved		Unimproved		Dead		
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	
Cholecystostomy	4	44.44	5	55.56					9
Cholecystectomy	3	100.00							3
Cholecystectomy and choledochostomy	2	100.00							2
Exploratory laparotomy					1	50.00	1	50.00	2
Appendectomy					1	100.00			1
Cholecystogastrostomy	1	100.00							1
Incision drain abscess pancreas	1								1
Removal pancreatic stone and pancreatic duct and pancreas drained	1								1
Total									20

spreading with the inflammatory process until the whole gland became involved. It might therefore be inferred that the induration begins usually in the head, spreading as the inflammatory process eventually involves the entire gland. The only exception to this course of events that occurred in our series was the one case in which the pancreatic stone was removed. In this instance the pancreas was indurated from the point at which the stone blocked the duct of Wirsung, distal to and including the tail, the head being perfectly normal in consistence. The stone was located at about the junction of the head and the body. Not only was this evident on palpation, but microscopic sections made of the tissue removed from the head and the

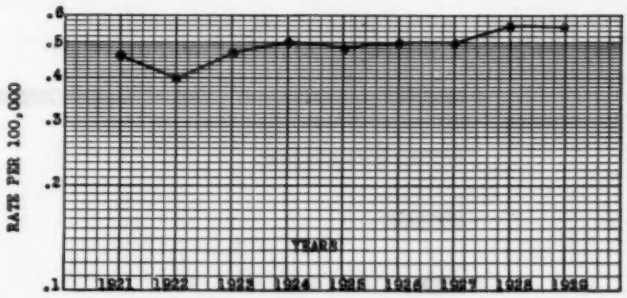

CHART 3. DEATH RATE FROM PANCREATIC DISEASES, OTHER THAN CARCINOMA AND DIABETES MELLITUS, IN THE REGISTRATION AREA OF THE UNITED STATES, 1921–1929

tail revealed the presence of an intralobular pancreatitis of the portion distal to the stone and a normal gland proximal to it. In the mortality statistics of the United States, deaths from disease of the pancreas are listed separately from carcinoma of the pancreas and diabetes mellitus. It is to be noted in tables 8, 9 and 10 that the ratio of the number of deaths recorded for the years 1921–1929 inclusive, in comparison with the population for the same years, remains practically constant (tables 8, 9 and 10 and chart 3).

OPERATION

Of the 20 patients all were submitted to operation. Nineteen recovered (table 11, chart 4) and one died. The immediate cause of

death of this patient was thought, and at autopsy was proved, to have been due to an acute dilatation of the stomach. The supposition was that this death was due to a high obstruction as a result of a gastro-mesenteric ileus. Only an exploratory laparotomy was made in this case and the abdominal cavity opened and closed, so that this death, while of course it must be taken into consideration, was unrelated to any operative procedure that could be considered specific for chronic pancreatitis. Of the remaining 19 patients who were treated specifically by surgical measures directed to alleviate the chronic inflammation present in the gland, all survived operation. In two, however, the condition remained unimproved after operation. In one of these merely an exploratory laparotomy had been performed,

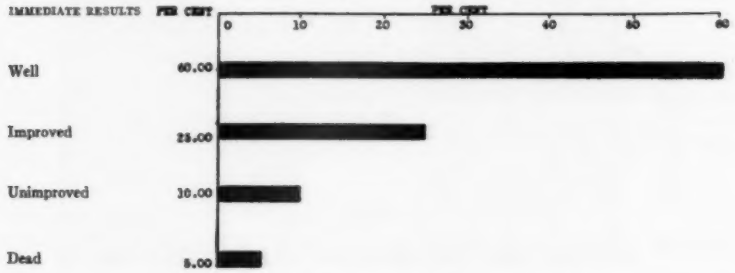

CHART 4. IMMEDIATE RESULTS IN 20 CASES OF CHRONIC PANCREATITIS. JOHNS HOPKINS HOSPITAL, 1891–1932

with no attempt to drain the affected area, and in the other the appendix had been removed. There was a lack of improvement in these two cases, so that counting the patient that died, on whom an exploratory laparotomy was performed, and these additional two, it would suggest that operative procedures not directed specifically toward drainage of the pancreas were, at least relatively, inefficacious. Of the remaining seventeen, in 9 cases drainage of the gall-bladder was performed. Of these patients 4 (44.44 per cent) were well after operation and 55.56 per cent improved. In three removal of the gall-bladder was accomplished, and of these three, all were well. In two, in addition to removal of the gall-bladder, the common duct was drained, and they have remained well since operation. In one a cholecystogastrostomy was performed; in another an incision was

made into a small cavity in the head of the pancreas, from which some grumous material was drained. Both of these patients had an uneventful recovery and remained well. In the remaining case a stone was removed from the duct of Wirsung and drainage established not only through this duct, but down to the pancreas as well. Thus it can be said, at least from this group of cases, although small, that by far the best results were obtained by operative procedures which

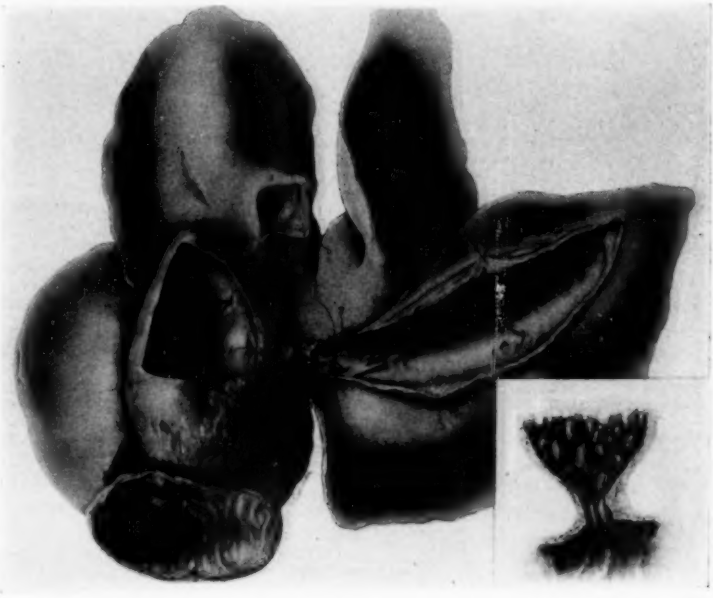

FIG. 1

were directed toward drainage of the biliary tract and thus indirectly of the pancreatic ducts. Of course, it must be understood that when one states that patients are well, one must qualify this by admitting that the follow-up study over a period of years has been very incomplete, and to really prove the efficacy of operative procedures directed to the relief of chronic inflammation of the pancreas one would have to compare the gland before and after operation, which is, of course,

impossible. The symptoms and signs, however, of which the patient complained, disappeared following operations effecting drainage of the biliary or the pancreatic ducts.

It might be well to add here a word of caution against the indiscriminate employment of cholecystogastrostomy. In support of this I need only refer to the experimental work of our own and others, in which cholescystogastrostomy was performed on animals, with the

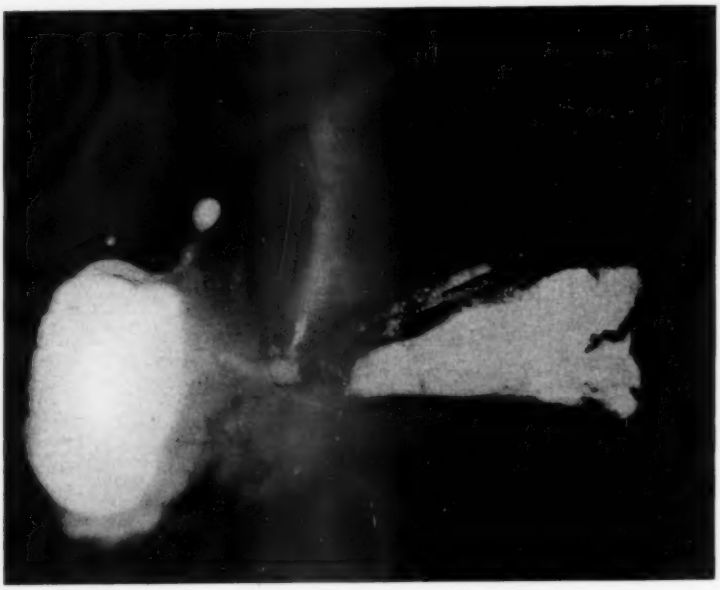

FIG. 2

result of producing not only diffuse infection of the bile and biliary tract, but also a diffuse hepatitis and even liver abscess. Figure 1 is a drawing of a specimen obtained from an abattoir in Baltimore in which there was an anomalous connection between what seemed to be the gall-bladder and the stomach of a pig. Figure 2 is an x-ray of the same. It is to be noted that the liver is literally packed, so to speak, with cinders and gravel. The powerful contractions of the stomach had been forcing the gastric contents into the hepatic ducts,

which as a result were distended and infected. This specimen seems to demonstrate the inefficiency of the hepatic ducts to prevent the

FIG. 3

entrance of foreign material into the liver when the common bile-duct does not end in the ampulla of Vater, under the protection of the

sphincter of Oddi. Undoubtedly the weaker peristaltic contractions of the duodenum also tend to prevent forcing of intestinal contents into the common bile-duct. Figure 3 is an x-ray of a patient in whom a similar anomaly was proved at autopsy. The patient died of an abscess of the liver. The injection of the biliary tract was accomplished during the diagnostic study when the patient was given barium by mouth for a gastro-intestinal x-ray series. The point to be emphasized is, that when the gall-bladder is anastomosed with the stomach, material from the stomach can be forced, by the vigorous gastric contractions, into the gall-bladder, and that this may result in permanent damage to the liver and biliary tract. In non-malignant conditions of the pancreas, cholecystogastrostomy should be avoided if possible. An anastomosis, if necessary, can be made between the duodenum and the gall-bladder with greater ease, if the first and second parts of the duodenum are slightly mobilized, thus having the pyloric sphincter to protect the gall-bladder from the more powerful contractions of the stomach. It would also seem to be a good practice, when dealing with instances of localized indurations of the pancreas, particularly in the head, to explore them directly by incision or at least by needle puncture, for it is probable that, in some, pancreatic stones or localized sterilized abscesses will be found. It is well known that undoubtedly many cases of this nature have been mistaken for carcinoma, and the patients have remained well after a purely palliative operation. Direct surgical exploration of the gland in cases of chronic pancreatitis is not difficult or necessarily dangerous because of the fact that as a rule the scarring in the gland is so pronounced, and the fibrous tissue substitution, as a result of chronic inflammation, is so diffuse, that the gland bleeds relatively slightly and the tissue will hold ligatures securely. Suture of the chronically inflamed gland is accomplished much more easily than in the normal pancreas in cases of acute pancreatitis. So that it is possible, in these cases in which there is doubt as to the proper operative procedure, to explore the pancreas without fear of hemorrhage or the escape of pancreatic ferments, and thus determine, deliberately and more accurately, the type of pathological lesion with which one has to deal. For it would obviously be inadvisable to submit a patient to the hazard of chronic hepatitis with a possibility of cirrhosis

hepatis later on, or chronic infection of the biliary tract, with the possible formation of a liver abscess following cholecystogastrostomy, if the chronic pancreatitis could be treated in a more simple manner. In the case of pancreatolithiasis herein reported a good result was obtained by the very simple and easy removal of a stone from the duct of Wirsung, whereas all the palliative operations, above mentioned, as well as drainage of the biliary tract would have been totally inefficacious in this instance. In other words, the presence of stones, or localized abscesses in the head of the pancreas, should be eliminated as a possible cause of the chronic pancreatitis in every instance, before resorting to one of the above-mentioned palliative operative procedures. In the absence of such affections, however, drainage of the biliary tract should be established. If the patient is jaundiced and malignancy cannot be entirely excluded it would seem advisable to perform a cholecysto-duodenostomy, if feasible.

NEOPLASMS OF THE PANCREAS

In this series of 167 cases of diseases of the pancreas 110 were new growths. In one patient the tumor was benign, an adenoma of the islands of Langerhans. In view of this being the only instance of such a growth in the records of the Johns Hopkins Hospital, and of the detailed clinical and post-mortem study that was made of the case, it is felt that a detailed report would prove both interesting and instructive.

Unit History 25,417, R. P. J., *aet.* 39, male, white, married.

Admitted: June 24, 1929. Medical Service.

Complaint: Attacks of dizziness, weakness, sweating, associated with unconsciousness.

Family history: Negative.

Past history: Negative.

Present illness: Patient enjoyed excellent health until two years ago, when upon applying for life insurance he was informed that he had high blood pressure. Eighteen months ago he began to have attacks of weakness, dizziness, with a swimming sensation in the head. He was told by friends that he staggered as if drunk. About one year ago the attacks became more frequent and were associated with periods during which the patient was only semi-conscious. Later on (six months ago) the attacks were accompanied by a total loss of consciousness. These attacks came on at first, as a rule, in the early morning before the patient arose from his bed for the day, but soon they occurred once or twice during the

day as well. Typical attacks, described by the patient and his wife, are said to have begun with a feeling of extreme weakness, dizziness and sweating, accompanied by a peculiar fixation of the facies, resulting in an expression of staring. At this time the patient was semi-conscious, groaned, and talked a great deal without present or later knowledge of what he had said, talking very much like a person in a pronounced state of alcoholic intoxication. As the attack progressed, muscle groups began to twitch, such as those supplying the mouth, arms and hands. The patient became very restless, went into a profound coma, with marked generalized convulsions, somewhat more pronounced on the left side. Loss of control of the vesical sphincter occurred several times, but never of the rectal. The attacks as a rule occupied approximately one-half hour, when the patient recovered spontaneously. The sequelae were headache and a marked subjective feeling of fatigue. Occasionally the attacks would be aborted spontaneously, the patient regaining consciousness before going into the state of convulsion. Although there was no hunger or desire for food, the patient discovered that orange juice and milk would abort an attack. In spite of the fact that he was completely unaware of his surroundings, he would respond to a command to drink orange juice and milk. During the past year patient has gained twenty-five pounds in weight.

Physical examination: Temperature 99. Pulse 100. Respirations 22. B. P. 195/130. Patient well developed and well nourished. Pronounced diminution of hearing. Heart slightly enlarged to left. Otherwise physical examination negative.

Laboratory Findings: W. B. C. 8,200. R. B. C. 4,730,000. Haemoglobin 92%. C. I., 1.0.

Differential normal. Wassermann negative.

Blood Chemistry: N. P. N. 36 mgm.%. Uric acid 3.6 mgm.%. Sugar 6.0 mgm.%. Calcium 9 mgm.%. Phosphorus 3.7 mgm.%. Guanidine 0.15 mgm.%. Creatinin 2.6 mgm.%.

X-ray: Heart enlarged; dilated aorta.

Phthalein, intravenous: First hour, 300 cc., 35%; second hour, 250 cc., 15%; total, 550 cc., 50%.

Urea clearance greatly reduced. Blood urea nitrogen—19.

Electrocardiogram: Normal.

Glucose Tolerance Curve: That of a diabetic glucose tolerance curve. 200 grams of glucose given on fasting stomach at 8:30. Readings of blood sugar curve:

	(1)	(2)
8:30 a.m.	4 mgm.%	4 mgm.%
9:00 a.m.	167 mgm.%	5 mgm.%
9:30 a.m.	229 mgm.%	142 mgm.%
11:30 a.m.	248 mgm.%	150 mgm.%

Patient in midst of an attack when specimen was taken. First reading of 4 mgm. seemed absurdly low, but test repeated several days later given under table 2.

Blood sugar readings under ordinary circumstances on ward, and not on fasting stomach were: 8:30 a.m., 43 mgm.%; 9:00 a.m., 45 mgm.%; 9:30 a.m., 44 mgm.%. The blood sugar stays around 50 to 60 mgm.% normally, and gradually falls until patient begins an attack, usually below 40 mgm.%. Adrenalin hypodermically, or glucose and orange juice by mouth, have an instantaneous beneficial effect. Pituitrin had no effect. Thyroid extract in doses of 1 grain twice each day seem to improve patient's sense of well-being and lessen number of attacks.

Diagnosis: (1) Spontaneous hypoglycaemia; probable adenoma of islets of Langerhans. (2) Hypertension. (3) Chronic nephritis.

Operation: Partial pancreatectomy. When the abdomen was explored the operator was unable to see or feel any abnormality in the pancreas. Neither on the anterior or posterior portion was there anything suggestive of a tumor of the pancreas. Approximately half of the pancreas was removed by resection of the tail and about half of the body of the gland.

In spite of post-operative treatment of continuous intravenous glucose, adrenalin and other general measures to combat shock, the patient succumbed the following morning. Blood sugar rose immediately after the operation to 92 mgm.%. Blood pressure continuously fell from 210/150 to 80/60 in five hours after operation. Post-operative reaction was more like delayed surgical shock than one of hypoglycaemic reaction.

Autopsy report No. 11035, Dr. Frank Kindell.

Anatomical diagnosis: Adenoma of islands of Langerhans in head of pancreas; resection of tail of pancreas, fresh operative wound; fresh thrombosis in splenic vein and artery; syphilitic aortitis; generalized arterio-sclerosis of the aorta; scarring of kidneys; and cardiac hypertrophy.

Gross findings: (1) Heart enlarged. (2) Thymus increased in amount. (3) Pancreas: Greater part of tail removed. Remainder weighs 35 grams. On external examination and several sections it seems to be a normal pancreas. There is slight discoloration of the tissue along the line of incision in the autopsy specimen, but no extensive necrosis. This portion of the pancreas is cut up into many thin slices. It is quite normal in appearance, except for a nodule of tissue about the size of a dime, 22 x 12 x 9 mm., in that portion of the head of the pancreas which is attached to the duodenum. This tumor mass is sharply circumscribed, softer than the remainder of the pancreas, and on section slightly pink in color. It is quite friable, and the cut surface shows no definite structure. The tumor could not be seen on the anterior or posterior surface of the pancreas, nor could it be felt. The consistence on palpation was indistinguishable from normal pancreatic tissue. The tumor tissue weighed about 2 grams. The pancreatic duct was normal. There was no accessory pancreatic tissue revealed after a most careful search.

Microscopic findings: Thymus: There is a good deal of thymus tissue in lobules separated by fat. There are rather numerous masses of lymphocytes in the periphery of the thymic lobules.

Spleen: There are a few areas of suspected necrosis. Some hemorrhage about Malpighi's bodies.

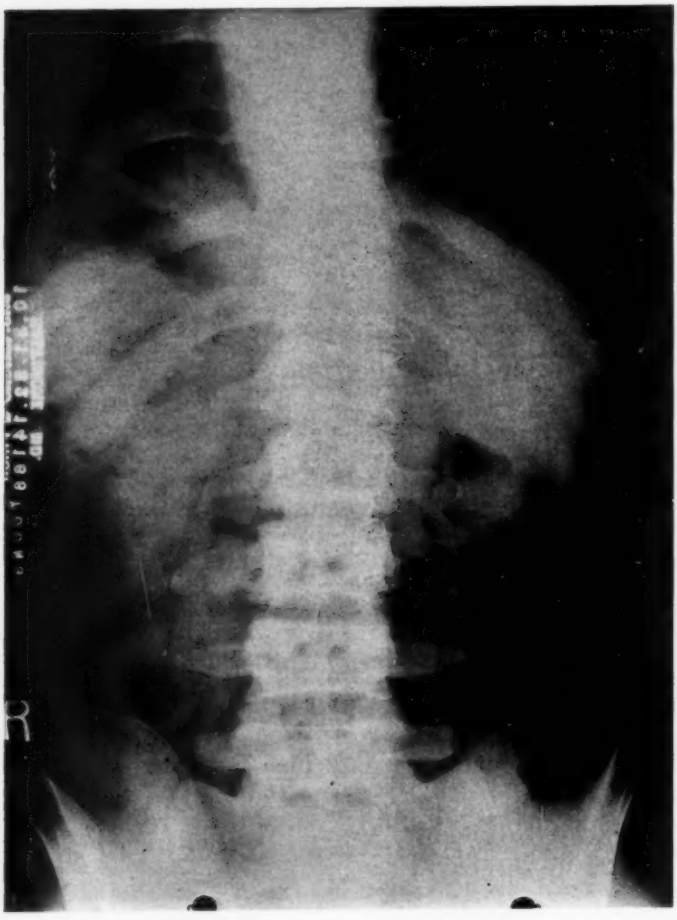

FIG. 4

Stomach: Scattered lymphoid germinal centers in mucosa.

Pancreas: Numerous blocks. Infection and necrosis near site of operation, and in this material there are swarms of bacteria, small Gram plus cocci. There

are scattered fresh fat necroses. Also scattered hyaline arterioles. Pancreatic tissue itself appears normal. The islets of Langerhans are also normal in pancreas. Granules in islands stain readily, appear best in sections stained with neutral ethyl violet. Only the cells with the staining reaction to the Beta cells can be demonstrated.

Tumor: The small tumor is shown by several blocks fixed like the pancreas by a variety of methods. The tumor is made up by cords of small cells separated by a capillary network (figure 4). There are numerous, rather good-sized arteries and veins, but these are not surrounded by any appreciable amount of connective tissue. The cells have rather deep-staining small nuclei and only a moderate amount of cytoplasm. There are very few mitoses. The cells are polygonal in outline and arranged in cords two cells in thickness. The cytoplasm is faintly granular. The cells somewhat resemble those of the islands of Langerhans. All the special stains for demonstrating specific granules have been so far unsuccessful. An extract was made from the greater part of the tumor, but when injected into rabbits caused only a slight fall in blood sugar. It is probable that the method of extraction was not the best one for the purpose.

Liver: Liver cells show a certain amount of fat. There is very slight central atrophy with pigmentation of cells about central veins. This pigment does not stain for iron. Glycogen stain shows liver contains almost no glycogen. Only an occasional cell contains a few red-staining granules. The leucocytes in the liver capillaries contain no granules.

Adrenals: No lesions. There are rather numerous hyaline arterioles in the capsule.

Kidneys: Numerous lymphocytes.

Testes: No lesions. Also thyroid.

Parathyroids: Numerous clumps of pink-staining cells.

Hypophysis: Tissue well preserved. There are more anterior lobe cells extending back into the posterior lobe than usual. Two sections show tiny nodules in the anterior lobe, which appear to be adenomata. In the granule stain these little tumor masses contain no granules. With ordinary stains these cells stain more deeply than others.

Muscles, kidney and heart show very little glycogen.

Tumor in the case suggests an adenoma.

Dr. Wm. G. MacCallum's note: The organs of internal secretion examined show the persistence of the remains of the thymus which are not quite normal looking. The suggestion arises that there is a new formation of the more lymphoid cells in a tissue which is much more rarified, and which still contains Hassall bodies. Thyroid and parathyroid glands appear normal. Hypophysis shows an excess of basophilic cells, and there are masses of basophilic cells invading more than normally the posterior lobe Otherwise no marked abnormality. The tumor imbedded in the pancreas shows a framework of fairly coarse trabeculae of connective tissue, rather widely separated, and then a very delicate network of cells

which do resemble those of the islands of Langerhans. They do not show the Beta granules, but stain pretty uniformly red, suggesting the Alpha granules. This appears to be one of the very few cases recently described in which hyperinsulinaemia has resulted from a tumor apparently composed of island of Langerhans tissue.

Comments: From a surgical standpoint this case is of particular interest, mainly because of the impossibility at operation of discovering the tumor buried in the head of the pancreas, either by visualization or palpation. The consistence of the adenoma was similar to that of the surrounding parenchyma, and even when the gland was removed at autopsy the tumor remained unrevealed until serial cuts through the head of the pancreas were made. Even had the location of the adenoma in the head of the pancreas been known, its safe removal would most surely have been precluded. It is also evident that removal of a large portion of the remaining and normal gland, in order to modify the course of the disease, is inefficacious unless by sheer luck the excised tissue contained the tumor, which is rather problematical. These adenomata are more frequently found towards the head region of the pancreas. Furthermore, the mortality associated with partial pancreatectomy must necessarily be high, and when considered together with the lack of improvement in similar cases reported in the literature, would seem to condemn the operative removal of a portion of the pancreas for hyperinsulinaemia unless the portion to be removed can be shown to contain the tumor tissue. When a tumor of the pancreas can be seen or felt in these cases one is justified in removing it, regardless of its position, for these adenomata are as a rule small, and their excision, if located in the head of the pancreas, would not interfere with the circulation of the surrounding duodenum, the most to be feared complication. The blind removal of a large portion of the normal gland has no effect on the function of the remaining adenoma of the islands of Langerhans if left behind and is an operation that should be abandoned. The patient herein described could not have been cured medically or surgically, unless a total pancreatectomy had been performed, which in this case at least would have been impossible. It is therefore pointed out that, although a clinical diagnosis of adenoma of the islands of Langerhans was made, discovery and removal of the tumor at operation were impossible. It is to be emphasized, that in the event a definite tumor of the pancreas cannot be seen or felt and removed, it is preferable to close the abdomen and treat the patients symptomatically by medicinal measures, rather than subject them to the hazards of partial removal of the pancreas which so far has proved inefficacious.

Of the malignant tumors of the pancreas there were 109, forming 65.27 per cent of the total number of cases in this series. This group consisted entirely of cases of carcinoma, there being no instance of sarcoma of the gland. The symptoms of carcinoma of the pancreas depend, of course, on the location of the tumor in the gland and vary

accordingly. These manifestations in fact are mainly reflected disturbances of contiguous structures and organs (table 12, chart 5). It is, of course, obvious that when the growth occupies the head of the gland it will before long interfere with the bile-ducts. On the other hand, the body and tail of the pancreas being the "silent areas," a growth may become extensive enough to be palpable on abdominal examination before the patient is aware of his inability to follow his daily routine. In many instances the patients may discover the tumor themselves. The clinical characteristics of growths involving the body of the pancreas are therefore somewhat indefinite. General

TABLE 12

Signs and symptoms of patients having carcinoma of the pancreas, Johns Hopkins Hospital, 1891–1932

SIGNS AND SYMPTOMS	NUMBER OF CASES	PER CENT
Pain	95	87.16
Loss of weight	94	86.24
Jaundice	76	69.72
Nausea and vomiting	72	66.06
Diminution of pigment in stools	64	58.72
Weakness	47	43.12
Bilirubinuria	46	42.20
Itching	36	33.03
Constipation	30	27.52
Pigmentation of skin	17	15.60
Gall-bladder diseases	11	10.09
Cyanosis	6	5.51
Diarrhoea	5	4.59

and progressive deterioration of health, anaemia, general weakness, anorexia, increased susceptibility to fatigue, rapid and pronounced loss of weight, with no essential change in the bowel movements, made up the main clinical features of the group of these cases encountered in the Johns Hopkins Hospital. In the patients in whom the head of the gland was affected, in addition to the above-mentioned signs and symptoms there were those produced by compression of the common bile-duct, in particular a progressive, unmitigating jaundice, not associated with elevations of temperature, but in conformity with Courvoisier's law there was in the majority of cases distention

of the gall-bladder. Enlargement of the liver was also invariably present, and at times a lappet of the right lobe would be pulled down by the enlarged gall-bladder to such an extent that it could be distinctly felt through the thin walls of the abdomen of an emaciated individual.

While it is frequently stated that pain in such cases is conspicuous by its absence, it was not so in the Johns Hopkins series. It was one of the outstanding clinical features in 95 cases (87.16 per cent), being located in the epigastrium; in 94 (86.24 per cent) there was an extreme loss of weight, and in 72 (66.06 per cent) nausea was pronounced.

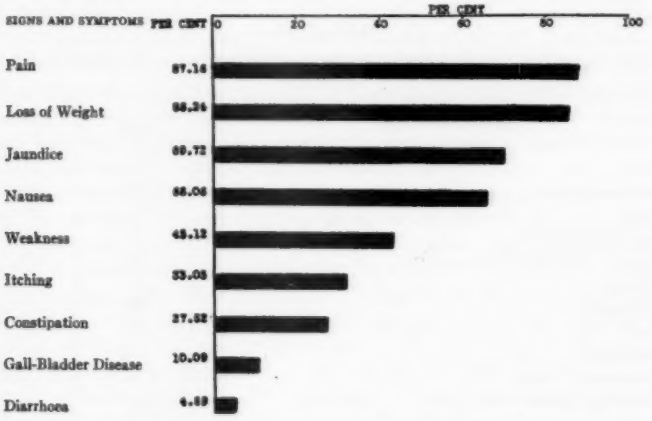

CHART 5. SIGNS AND SYMPTOMS OF THE 109 PATIENTS HAVING CARCINOMA OF THE PANCREAS. JOHNS HOPKINS HOSPITAL, 1891–1932

In 47 (43.12 per cent) a little less than half complained of weakness and only 36 of the 109 patients, or 33.03 per cent, had pruritus from the jaundice. In 11 (10.09 per cent) there was a previous history of gall-bladder disease, either a history of jaundice, gall-bladder attacks, or operations upon the biliary tract. In only 5 cases, or 4.95 per cent, was there diarrhoea. In 86.24 per cent there was an extreme loss of weight. In 58.72 per cent the stools were clay-colored; in 23 cases (21.10 per cent) there was blood in the stools; in 42.20 per cent the urine contained bile. The skin was pigmented in 15.6 per cent in addition to the 69.72 per cent who were jaundiced. This pigmenta-

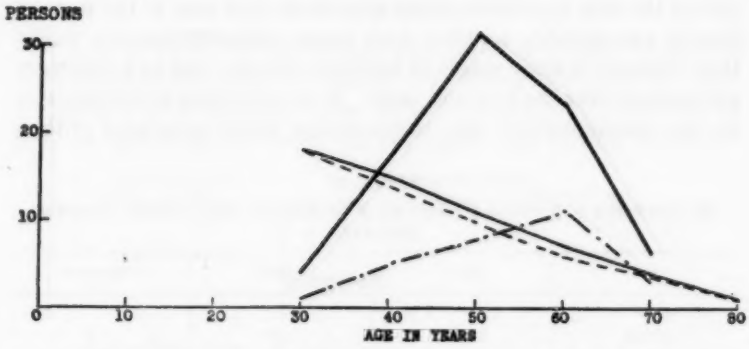

CHART 6. SHOWING IN A GROUP OF 109 ADULTS TWENTY-FIVE YEARS OF AGE AND OLDER THE EXPECTED NUMBER OF MALES AND FEMALES IN EACH TEN-YEAR AGE GROUP, AND THE ACTUAL NUMBER OF MALES AND FEMALES HAVING CARCINOMA OF THE PANCREAS IN THESE SAME AGE GROUPS

Expected number of males ————. Actual number of males ————.
Expected number of females ----------. Actual number of females —·—·—·—.

In regard to the age distribution of the males, in the carcinoma group, there is an apparent maximum at the age of 50. This, however, is apparent only and not actual, due to the decrease in each succeeding ten-year-age group. The 23 in the age group 55–64 years is a larger percentage than the 31 in the age group 45–54 years, for the former group contains only 6.1% of the population and the later 10%. Therefore, the rate increases from 30 years on, reaching a maximum at about 60 years.

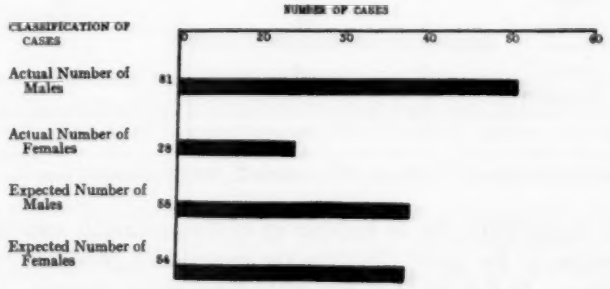

CHART 7. DISTRIBUTION OF 109 CASES OF CARCINOMA OF THE PANCREAS WITH REGARD TO SEX, THE EXPECTED NUMBER OF EACH SEX IN A SAMPLE OF 109 PERSONS PICKED AT RANDOM FROM THE REGISTRATION AREA OF THE UNITED STATES

tion of the skin was similar in all respects to that seen in the cases of chronic pancreatitis, a rather dark brown pigmentation not unlike that observed in early stages of Addison's disease, and as a rule more pronounced over the face and neck. It is interesting to speculate as to the possibilities of this pigmentation being associated with a

TABLE 13

*Age distribution of 109 cases of carcinoma of the pancreas, Johns Hopkins Hospital, 1891–1932**

AGE	MALES	FEMALES	BOTH SEXES
years			
25–34	4	1	5
35–44	17	5	22
45–54	31	8	39
55–64	23	11	34
65–74	6	3	9
Total.....	81	28	109

TABLE 14

*Age distribution of males and females in a sample of 109 adults (twenty-five years of age and older) taken at random from the Registration Area of the United States**

AGE	MALES	FEMALES
years		
25–34	18	18
35–44	15	14
45–54	11	10
55–64	7	6
65–74	4	4
75 and over	1	1
Total.....	56	53

* Based on the figures of 1910 and 1920, volume II, 1920, Population, page 56.

chronic pancreatitis due to backing up of the pancreatic secretion in the portion of the gland distal to the obstruction produced by the carcinoma. In 6 cases (5.51 per cent) there was a cyanosis, but as these patients were extremely ill and in the late stages of the disease, it is a question whether this cyanosis was pancreatic in origin or due to their almost moribund condition.

AGE DISTRIBUTION

It is to be noted that the disease did not occur in this series prior to twenty-five or later than seventy-four years of age (table 13); that it increases to its maximum from forty-five to sixty-five, reaching its peak at approximately sixty for both male and female (table 13,

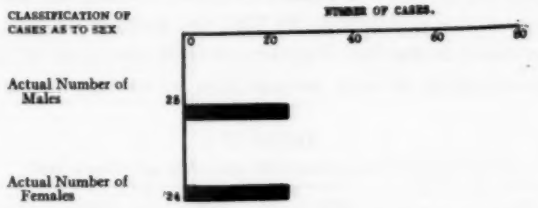

CHART 8. DISTRIBUTION OF 49 CASES OF NON-CARCINOMATOUS DISEASES OF THE PANCREAS WITH REGARD TO SEX

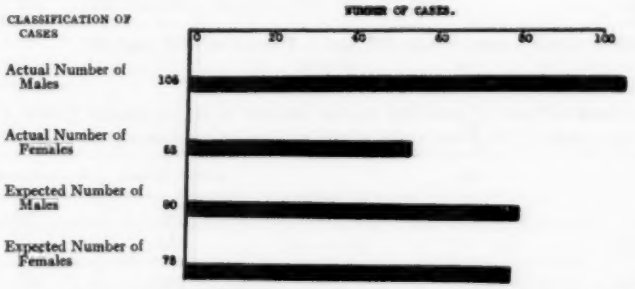

CHART 9. DISTRIBUTION OF 158 CASES OF SURGICAL DISEASES OF THE PANCREAS, WITH REGARD TO SEX; EXPECTED NUMBER OF EACH SEX IN A SAMPLE OF 158 PERSONS, PICKED AT RANDOM FROM THE REGISTRATION AREA OF THE UNITED STATES

chart 6). The incidence is about three times as frequent in men as in women (chart 7), whereas the proportion of men to women in the population as a whole, considering a similar sample, *i.e.*, of 109 people, is about half and half. In other words, there are about the same number of men as women, but in the 109 patients affected with carcinoma of the pancreas the men are victims of the disease out of proportion to their normal incidence in the population. There is also to

be noted an age selection, in that there are a great many more people between the ages of forty-five and sixty-five affected with carcinoma than would normally occur in a similar sample of the population as a whole between these ages (tables 13 and 14, chart 7). These figures were derived by applying the percentages for the corresponding age groups given in the United States Censor's Volume for the age-sex distribution of the population, to 109, the number of actual cases. It is to be noted in the bar diagrams that in the cases of acute and chronic pancreatitis there is no selection as to sex, the occurrence

TABLE 15

*Population of United States, 1920 and 1930, according to sex**

SEX	1930	1920	TOTAL	PER CENT
Males	62,137,080	53,900,431	116,037,511	50.8
Females	60,637,966	51,810,189	112,448,155	49.2
Total	122,775,046	105,710,620	228,485,666	100.0

* United States Census, volume III, part 1, Population 1930, page 20.

TABLE 16

Actual number of cases of pancreatic diseases classified as to sex; expected number of each sex in a sample of 158 people picked at random from the population of the United States

SEX	ACTUAL NUMBER	EXPECTED NUMBER
Males	105	80
Females	53	78
Total	158	158

being as frequent in men as in women (chart 8). However, in chart 9, tables 15 and 16, a comparison of the entire group of pancreatic affections, with a sample of the population of the United States reveals a predilection for males. It is interesting to note that although the pancreas is a deeply seated gland, and the opportunity to palpate tumors of the pancreas are, of course, therefore made very much more difficult, the lapse of time between the onset of symptoms and operations in cases of the disease of the pancreas, particularly carcinoma, in the majority of cases was less than three months (table 17, chart 10).

This after all is quite a good record, for in the majority of malig-

nant diseases affecting the abdominal viscera procrastination in entering the hospital is more pronounced. The location of the tumor

TABLE 17

*The lapse of time between the onset of symptoms and operation in the cases of disease of the pancreas, Johns Hopkins Hospital, 1891–1932**

INTERVAL BETWEEN ONSET OF SYMPTOMS AND OPERATION	TYPE OF PANCREATIC DISEASE			
	Carcinoma of pancreas		Non-carcinomatous pancreatic diseases	
	Number	Per cent	Number	Per cent
months				
1–3	43	41.35	21	47.73
4–6	26	25.00	4	9.09
7–9	11	10.58	4	9.09
10–12	11	10.58	2	4.54
13–15	3	2.88	4	9.09
16–18	2	1.92	3	6.82
19–21				
22–24	5	4.81	2	4.54
25 and over	3	2.88	4	9.09
Total.....	104	100.00	44	100.00
*Unknown.....	5		5	
Total.....	109		49	

TABLE 18

Location of the tumor in carcinoma of the pancreas in 109 cases at the Johns Hopkins Hospital, 1891–1932

LOCATION OF CARCINOMA	NUMBER OF CASES	PER CENT
Head of pancreas.....	75	86.21
Body of pancreas.....	3	3.45
Tail of pancreas.....	3	3.45
Entire length of pancreas.....	6	6.90
Total.....	87	100.01
Unknown site.....	22	
Total.....	109	

in carcinoma of the pancreas in the 109 cases (table 18, chart 11) was found to be in the head of the pancreas in 86.21 per cent; 3.45 per

cent in the body, and 3.45 per cent in the tail. Carcinoma was diffuse in 6.9 per cent.

In this series of cases there has never been an attempt made to remove carcinoma of the pancreas by either total or partial pancreatec-

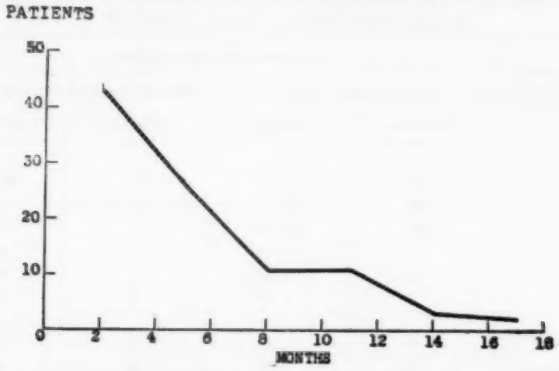

CHART 10. DISTRIBUTION OF THE CASES OF CARCINOMA OF THE PANCREAS ACCORDING TO THE LAPSE OF TIME BETWEEN THE ONSET OF SYMPTOMS AND OPERATION

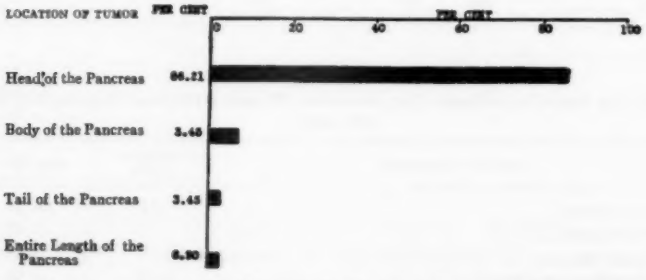

CHART 11. LOCATION OF THE TUMOR IN CARCINOMA OF THE PANCREAS IN 109 CASES. JOHNS HOPKINS HOSPITAL, 1891–1932

tomy. The mechanical difficulties are almost insuperable and even if boldness and good luck are added to the operative skill, the end hardly justifies the means. For unfortunately, by the time the patient begins to have symptoms of the affection, so many important contiguous structures have already been involved that nothing but

TABLE 19

*A summary of the operations performed upon 106 cases of carcinoma of the pancreas at the Johns Hopkins Hospital, 1891–1932**

TYPE OF OPERATION	NUMBER OF CASES	PER CENT
Exploratory laparotomy	40	37.74
Cholecystogastrostomy	34	32.08
Cholecystostomy	12	11.32
Cholecystenterostomy	7	6.60
Post-gastroenterostomy	4	3.77
Cholecystectomy	3	2.83
Choledochostomy	2	1.89
Omentopexy	1	.94
Gastrotomy	1	.94
Drainage of pancreatic abscess	1	.94
Closure of biliary fissure	1	.94
Total	106	99.99

* In two cases the type of operation was not reported; in the third case carcinoma of the pancreas was established by autopsy.

TABLE 20

*Immediate results from the operations for carcinoma of the pancreas at the Johns Hopkins Hospital, 1891–1932**

TYPE OF OPERATION	IMPROVED		UNIMPROVED		DEAD		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Exploratory laparotomy	2	5.00	25	62.50	13	32.50	40	100.00
Cholecystogastrostomy	20	58.82	4	11.76	10	29.42	34	100.00
Cholecystostomy	3	25.00	3	25.00	6	50.00	12	100.00
Cholecystoenterostomy	2	28.57	—		5	71.43	7	100.00
Post-gastroenterostomy	2	50.00	1	25.00	1	25.00	4	100.00
Cholecystectomy	—		1	33.33	2	66.67	3	100.00
Choledochostomy	2		—		—		2	
Omentopexy	—		1		—		1	
Gastrotomy	—		1		—		1	
Drainage of pancreatic abscess	—		—		1		1	
Closure of biliary fissure	—		—		1		1	
Total	31		36		39		106*	

* In two cases the type of operation was not given; and the third case was established as carcinoma of the pancreas by autopsy. All three patients were unimproved as far as the immediate results were concerned.

a palliative operative procedure has ever been considered. This is borne out in a study of the types of operations (table 19) which have been performed to alleviate the symptoms by the fact that in 37.74 per cent of the cases only an exploratory laparotomy was done because the condition was already inoperable. In 32.08 per cent a cholecystogastrostomy was performed, and this was by far the most efficacious operative procedure. In the group of cases in which only an exploratory laparotomy was done, as would be expected, there was no amelioration of the signs or symptoms, and 32.5 per cent of the patients succumbed to the operative procedure (table 20). As stated above, the conditions were inoperable to begin with. In the group in which cholecystogastrostomy was performed, 58.2 per cent, that is, over half, were improved, there being a rather high mortality of 29.42 per cent. Cholecystoenterostomy was performed on only seven patients (6.6 per cent) and two (28.57 per cent) of these were improved, whereas 71.3 per cent succumbed. It is, of course, obvious that cholecystoduodenostomy should not be attempted in cases of carcinoma of the pancreas, because the duodenum is frequently involved and bound down by the growth. Suturing it to the gallbladder would be not only difficult but insecure because of tension.

PANCREATIC CYSTS

Of pancreatic cysts there were 7, all of these being so-called pseudocysts or accumulations in the lesser peritoneal cavity. In all probability they resulted from inflammatory conditions arising in the pancreas. These were drained directly transperitoneally through the gastro-hepatic and gastro-colic omenta, and in all of the cases the patients recovered.

PANCREOLITHIASIS

Although there are quite a few instances of pancreatic calculi recorded in the medical literature, the aim of this report of a single case is not merely to record another instance of this malady, but to describe a case that has been followed over a period of ten years, and to place on record at least one more heretofore unmentioned etiological factor in the production of acute pancreatitis.

The patient, a colored man 33 years old, was admitted to the Surgical Clinic of the Johns Hopkins Hospital from the gastro-intestinal dispensary as a case of

acute pancreatitis. The patient was examined by Dr. Thomas R. Brown and his staff on June 23, 1922. His complaint was a most severe pain in the epigastrium, which extended through to the back below the left shoulder-blade. The past history revealed that he had suffered occasional attacks of cramps for a period of fifteen years. The present illness began about two years ago with sharp intermittent pains in the epigastrium, which were more severe at night. The pain was unrelieved by food and, although his appetite was good, the patient was afraid to eat because of the possibility of food producing the pain. At first the pains came on at intervals of two months, but later they became more frequent The pains became progressively more severe, radiating in the later attacks to both flanks. The attack would last from three to five days. The frequency of the attacks has become greater, from every two months until recently they occur every few days. The pain has been much more severe in the recent attacks and is accompanied by nausea and vomiting. The patient has been constipated, but otherwise the stools are not remarkable. In this present attack, which began today, the pain has been most excruciating and of fiercest intensity in the epigastrium. There has been continuous nausea and vomiting.

Examination: W. B. C. 10,400. Haemoglobin 76%. Temperature 97.6°. Examination revealed a slender, well developed but undernourished negro man, suffering intensely from pain in the abdomen. Recent loss of weight. Skin somewhat cold and clammy. Pulse rapid. Presses hand against epigastrium, is constantly moaning about pain in abdomen, extending to back, both flanks, lumbar spine and both shoulders. Abdomen rather full and distended. No abdominal inspirations, as walls are held rigid and tense. Increased rigidity above umbilicus. Palpation and percussion very painful to patient. Palpation of flank causes a referred pain above umbilicus. Definite tenderness in costo-vertebral angle on both sides. No demonstrable fluid.

Diagnosis: Acute pancreatitis.

Patient transferred for immediate operation.

Operation: Dr. Emile F. Holman, Resident Surgeon, Johns Hopkins Hospital. Anesthesia, ether. On opening of the abdomen the peritoneum was found to be very oedematous and engorged. There was an abundance of fine sero-sanguineous fluid. In the omentum and in places of the parietal and visceral peritoneum there were areas of fat necrosis, particularly about the pancreas. The pancreas itself was enlarged, hemorrhagic in appearance, and very hard in consistence. All the remaining viscera, *i.e.*, stomach, spleen, duodenum, gall-bladder, were normal, but blood vessels everywhere engorged. The omentum was adherent to the small intestine and peculiar grayish blue in color. The stomach was somewhat adherent to the posterior peritoneum of the omental bursa. The pulse was 150 and respirations around 50 a minute during the entire operation. A diagnosis of acute hemorrhagic pancreatitis was made at the operating table, and then the abdomen hastily drained and closed. Two drains were placed down to the pancreas through the gastro-colic omentum, and one to the foramen of

Winslow. The patient vomited on the table, aspirated some of the chyme, and developed a post-operative bronchopneumonia.

The convalescence was rather stormy, but the temperature, pulse and respirations, were restored to normal in a week. Nine days after the operation the patient began to drain large amounts of clear fluid containing no pancreatic ferments, and not irritating to the skin. This drainage persisted for three weeks and then ceased. The patient was pronounced well and discharged on the thirty-sixth day after operation. Thus the clinical impression of Dr. Thomas R. Brown and staff was confirmed by the diagnosis of acute hemorrhagic pancreatitis made at the operating table by Dr. Emile Holman.

One year later, September 23, 1923, the patient was readmitted to the Johns Hopkins Hospital, complaining of pain in the epigastrium of six months' duration. After the previous discharge from the hospital he had been free from all symptoms for six months, when he began to have a recurrence of all his previous signs and symptoms. The pain was exactly similar in all respects to the previous attack, not only in location, but in intensity and radiation. There was also a recurrence of vomiting. The attacks were mainly nocturnal, lasting four days or longer at a time, and coming on every three to six weeks. The most recent attack had lasted two weeks. Epigastrium remains tender after attacks. The patient has noticed that the stools have become light yellow and bulky. Objective examination was essentially negative, except for pronounced undernutrition, a well healed right rectus incision, and some slight epigastric tenderness.

Clinical diagnosis: Sub-acute pancreatitis.

X-ray: Plain plate negative. G. I. series, hypermotile stomach.

Examination of stool: Dr. A. R. Shands. Demonstrated the absence of pancreatic ferments in the stool.

Operation: Dr. William F. Rienhoff, Jr. Anesthetic, ether. Abdomen opened, excising old scar. Abdominal viscera normal, excepting pancreas, which was exposed through gastro-colic omentum. Pancreas slightly enlarged and indurated from the junction of the head and body back to and including the tail. The most anterior portion of the head was of normal consistence. At the beginning of the indurated portion there was a fluctuant area about 0.5 cm. in diameter. This was incised, and after cutting through about 1 cm. of parenchyma a cavity was entered, from which gushed about fifty cubic centimeters of clear fluid. Into this cavity a small bent probe was inserted to find out if an occluded duct could be demonstrated. The probe touched a hard stone-like substance, which was extracted without difficulty. It proved to be a pancreatic stone 1 x 1.5 cm. The probe could then be inserted anteriorly into a collapsed duct of Wirsung, and caudally into a very much dilated duct. A small piece of pancreatic tissue was removed from the head and tail of the gland for comparison The incision in the pancreas was closed with interrupted silk sutures which, owing to the presence of fibrous tissue in the parenchyma, held very well. The peritoneum and anterior rectus sheath were closed with a continuous suture of No. 1 silver

wire, the skin with a continuous subcutaneous suture also of silver wire. Two cigarette drains were inserted, which were removed in five days. The convalescence was uneventful and the patient was well and discharged from the hospital in fourteen days. Pancreatic ferments, according to Dr. Shands, were present in the stool on the day of discharge.

It has been possible to follow up the patient for nine years, as he lives nearby in Baltimore, and he is perfectly well. The continuous silver-wire sutures, however, have broken up into many small pieces, due to the normally bending over of the patient through the period of these nine years. He has had no more attacks of pain.

TABLE 21

*Immediate results of 158 operative cases of pancreatic diseases at the Johns Hopkins Hospital, 1891–1932**

IMMEDIATE RESULTS	DISEASES OF THE PANCREAS														TOTAL	
	Carcimona of pancreas		Chronic pancreatitis		Acute pancreatitis		Pancreatic cyst		Pancreatic abscess		Pancreatic apoplexy		Adenoma of pancreas			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Well			12	60.00	10	55.56	4	57.14	2		1		1		30	18.98
Improved	31	28.44	5	25.00	1	5.56	3	42.86							40	25.32
Unimproved	39	35.78	2	10.00											41	25.96
Dead	39	35.78	1	5.00	7	38.89									47	29.75
Total	109	100.00	20	100.00	18	100.00	7	100.00	2		1		1		158	100.01

* One of these was not treated, as it was decided that the patient would not be benefited by an operation. Carcinoma of pancreas definitely established by a previous operation.

This case demonstrates that acute hemorrhagic pancreatitis may be caused by a pancreatic calculus, which, so far as we are aware, has not been heretofore shown to have been an etiological agent in the production of this malady. Furthermore, the transition of an acute pancreatitis into a chronic form occurred as the result of the persistence of the blockage of the duct. The patient has remained well for almost a decade in spite of the fact that the greater part of his pancreas was destroyed and fibrous tissue substituted for the parenchyma. The ultimate pathological changes shown in the microscopic sections are those of destruction distal to obstruction of the duct with

dilatation of the latter associated with atrophy of the glandular parenchyma but, as would be expected, the islands of Langerhans remaining unaffected. This change following obstruction of the duct was demonstrated experimentally for the first time years ago by Dr. William G. MacCallum. Exploration by incision of the pancreas the site of chronic inflammation is more easily and safely accomplished,

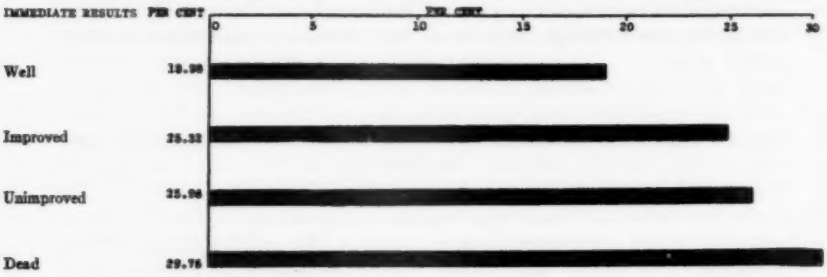

CHART 12. IMMEDIATE RESULTS OF 158 CASES OF SURGICAL DISEASES OF THE PANCREAS. JOHNS HOPKINS HOSPITAL, 1891–1932

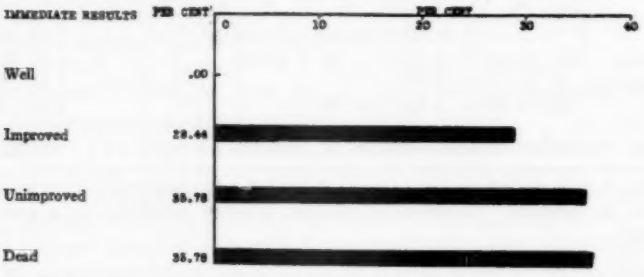

CHART 13. IMMEDIATE RESULTS IN 109 CASES OF CARCINOMA OF THE PANCREAS. JOHNS HOPKINS HOSPITAL, 1891–1932

because the scarred parenchyma does not bleed or secrete as readily as the normal and furthermore holds a suture more securely.

SUMMARY

The immediate results of 158 operative cases of pancreatic disease may be summarized as follows (table 21, chart 12).

Of the 18 cases of acute pancreatitis, ten or 55.56 per cent of the

patients were well, one or 5.56 per cent improved, and seven or 38.89 per cent died. In the cases of chronic pancreatitis, of which there were twenty, twelve or 60 per cent of the patients were well, five, or 25 per cent, improved, and two, or 10 per cent, were unimproved, one (5 per cent) died and in this patient, as stated before, death was due to a high intestinal obstruction which had really nothing to do with the operative procedure on the pancreas. In the carcinoma of the pancreas (chart 13) none of the patients were well; 31 (28.44 per cent) were improved, 39 (35.78 per cent) were unimproved, and 39 (35.78 per cent) died. Of cases of pancreatic cysts there were 7, four, or 57.15 per cent, of these patients were well, three or 42.86 per cent were improved, and none died. Of pancreatic abscess there were two cases. Both patients were well following operation. There was one case of pancreatic apoplexy, and one of adenoma of the pancreas; both patients succumbed to the operative procedure. A case is reported in which a pancreatic stone produced first an acute hemorrhagic pancreatitis to be followed after a year by a chronic pancreatitis. The stone was removed and the patient has remained well for a period of ten years.

ON THE ALLEGED TOXICITY OF COD LIVER OIL

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Although toxic effects following the administration of cod liver oil had been noted (1, 2) before the work of Agduhr (3) and Agduhr and Stenstrom (4), their extensive investigations of the cardiac lesions produced by the administration of small amounts of the oil to laboratory and farm animals have aroused considerable interest. The original observations were made on white mice, but the cardiac lesions found in these animals have likewise been stated to occur in all other animals employed (rats, cats, dogs, rabbits and calves), and even in children.

These observations are not without clinical bearing. Malmberg (5) reported two patients coming to autopsy with heart lesions similar to those described by Agduhr. The first patient, a premature girl, had received half a teaspoonful of cod liver oil twice a day, beginning at 3 weeks of age, and one teaspoonful twice a day, from 6 weeks till her death at 4 months. Degenerative and atrophic changes were found in the heart, with extensive connective-tissue proliferation which, in some places, penetrated the entire thickness of the myocardium. It is also interesting that the autopsy findings included: "acute pneumonia, hyperplasia lienis and rickets (craniotabes plus internal rachitic rosary)." Another premature infant with spina bifida cystica and complete paralysis of both lower extremities was fed supposedly large doses (15 to 20 cc. daily) of cod liver oil. The child lived 16 days, and at autopsy similar degenerative changes were found in the heart.

Henriksen (6) differs with Agduhr in the interpretation of his results. He states that the cardiac lesions which the latter characterizes as "transformation into connective tissue" are in reality examples of the more general phenomena, pigment atrophy and cellular regression,

and that such changes may result from endocrine or nutritional disturbances, toxins, infections, *etc.* He claims that overdosage with cod liver oil (1.4 gm. per kg. of body weight) causes cellular changes of a different type, characterized principally by increased liquid content of the tissues, and in the differentiated tissue by cellular regression. That such histologic changes are not specific is substantiated by Herlitz, Jundell and Wahlgren (7) who found lesions of the heart, as described by Agduhr, after feeding mice either egg-yolk, cod liver oil, irradiated or unirradiated ergosterol, or after direct irradiation of the animals.

Höjer (8) criticises the diets used by Agduhr as being deficient in vitamin B, and claims that heart changes induced by cod liver oil may be prevented by the addition of yeast to the diet. The relation between the toxicity of cod liver oil and vitamin B was first brought out by Plimmer and Rosedale (9) who found excess of cod liver oil injurious to chickens unless "balanced" by an increased marmite allowance. Harris and Moore (10) compared the growth curves of rats fed a diet containing 15 per cent of cod liver oil or arachis oil, with graded additions of vitamin B, and found at the intermediate levels of vitamin B intake that growth on cod liver oil was much inferior to that on arachis oil, but that at the higher level of B-intake, the growth curves of the two groups were analogous. This is confirmed by the recent work of Norris and Church (11).

These investigators cite the work of Gautier and Mourgues (12) and of Hawk (13) that cod liver oil may contain a whole series of toxic amines. Norris and Church fed isoamylamine and choline (the nitrogenous base of lecithin) to rats in the amounts that would have been ingested if cod liver oil had contained the amounts of nitrogenous base found by the earlier investigators. They found the same gross symptoms as those presented after administration of one of their oils; these symptoms were prevented or cured by the addition of extra yeast to the diet.

This toxicity of cod liver oil must be considered apart from hypervitaminosis D, since the dosage of cod liver oil necessary to induce pathological calcification, as a result of the antiricketic vitamin, would have to be calculated in liters. The amounts of cod liver oil which have been employed in the various investigations of this nature have

TABLE I

Amounts of cod liver oil fed in toxicity experiments

INVESTIGATOR	REFERENCE	ANIMALS USED	AMOUNT COD LIVER OIL PER KGM. BODY WEIGHT	REMARKS
Agduhr	(3, 4)	Mice	0.1–10 cc.	All levels produced heart lesions and electrocardiographic changes.
		Calves	0.1–1.6 cc.	
		Dogs, cats and pigs	0.1 cc.	
		Rats	0.5–12 cc.	Resistant to C. L. O. but greatest change induced by smallest dosage.
		Rabbits	2.0–5.0 cc.	Sensitive to C. L. O. Changes extensive.
Höjer	(8)	Rats	0.5–2.0 cc.	Changes attributed to vitamin B deficiency.
Herlitz *et al.*	(7)	Mice	3.3–10 cc.	Heart changes produced by C. L. O. also produced by irradiated or unirradiated ergosterol, ultra violet light, and egg yolk.
Henriksen	(6)	Rats	0.01–1.4 gm.	Changes characteristic of other vitamin and endocrine deficiencies.
Malmberg	(5)	Premature infants	4.0–6.0 cc. (1) < 14 cc. (2)	Heart changes similar to those produced in experimental animals.
Hartwell	(16)	Rats	16 gm.*	Inferior growth when compared with butter.
Harris and Moore	(10)	Rats	22–24 gm.*	Inferior growth when compared with arachis oil with graded vitamin B additions to diet.
Norris and Church	(11)	Rats	2.5 gm.*	Loss of weight relieved by addition of extra yeast.
Cox and Roos		Rats	27.3 gm.	No heart lesion but subnormal growth.

* These values were calculated on the assumption that the rats weighed 50 grams, and ate an amount of the diet which would correspond to about 30 calories.

varied enormously, as is indicated in table 1. Agduhr finds histological and electrocardiographic changes in most of his animals with a daily intake of 0.1 cc. of oil per kilo of body-weight.[1] No other worker has found deleterious effects at such levels, unless the diet was intentionally deficient in some other factor. The present communication shows that with an average daily intake of 27.3 gms. of cod liver oil per kilo of body-weight, for a period of 130 days, there are no demonstrable heart lesions induced in rats.

EXPERIMENTAL

In the course of an investigation of the nutritive value of individual fatty acid esters, cod liver oil was used as one of the mixed glycerides. The plan was to feed the oil in large quantities, and accordingly the diet was so designed as to furnish 78 per cent of the calories as cod liver oil. No provision was made to furnish extra vitamin B, as it had been found that 5 per cent of a potent brewer's yeast gave normal growth when other fats were used. The diet consisted of 20 per cent casein (washed repeatedly with 0.2 per cent acetic acid), 13 per cent maize starch, 56 per cent cod liver oil,[2] 6 per cent Osborne-Mendel salt mixture (14), and 5 per cent dried, powdered brewer's yeast. This diet was complete with respect to protein, salts and vitamins. When lard was used as the fat constituent of this diet (55 per cent, with 1 per cent cod liver oil, to supply vitamins A and D), normal growth was obtained. The oil was incorporated in the diet by first making a starch paste with a measured amount of water, whipping in the other constituents with an electric mixer and cooling rapidly. The diet was kept in the ice-box when not in use and freshly prepared not less often than every two weeks.

Four rats, two males and two females, reared on Bills' modification

[1] This accounts for Agduhr's recent recommendation (18) of 0.5–1.0 cc. of cod liver oil daily to children, to be discontinued after a month. One must wonder, in the light of clinical studies on rickets even when ten or twenty times this dosage is used, what would be the antiricketic value of the treatment.

[2] Two types of cod liver oil were used in this investigation. One, furnished by Mead Johnson and Co., Evansville, Ind., was rendered from livers of Newfoundland cod, and the other, purchased in the open market, reputedly rendered from Norwegian cod. No significant difference was noted in the behavior of the rats on the different oils.

of the Steenbock stock diet (15) were placed on each experimental diet at about 4 to 5 weeks of age. (Three groups of 4 rats each were fed the cod liver oil diet.) They were kept in a screen-bottomed wire

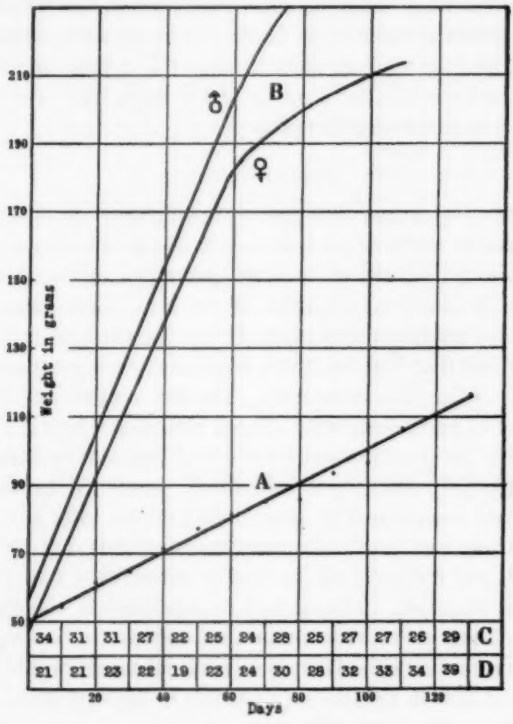

FIG. 1. Average weight curves of rats fed a synthetic diet containing 56 per cent fat:

A. Average for 12 rats receiving cod liver oil as the fat.

B. Average for 2 ♂ and 2 ♀ receiving lard as the fat.

C. Average grams cod liver oil ingested per kilogram body weight per rat per day, calculated in 10-day intervals.

D. Average caloric intake of cod liver oil rats, per rat per day, in 10-day intervals.

cage and allowed to eat of the diet *ad libitum*. Because of the nature of the diet, the food cups were emptied and refilled each day—record being kept of the food consumed. Although some slight spilling of

the food occasionally took place, this was reduced to a minimum by the use of special food cups.

The rats lived for the length of the experiment, 130 days, and gained weight slowly though at a sub-normal rate. They were obviously in a very poor state of nutrition, lethargic and dull, and their hair was of a sickly, yellow color. There was no sign of paralysis or other abnormality of gait.

The average weight curve of the animals receiving cod liver oil and the average caloric intake per rat per day for each 10-day period, together with the calculated intake of cod liver oil per kilogram of body-weight are presented in fig. 1. The caloric intake of two other groups of rats which grew normally on different fats, but which were kept under otherwise identical conditions, were 32.1, 35.7, 36.6, and 23.5, 31.8, and 36.0, respectively, for 3 consecutive 10-day periods. Part of the failure to grow more rapidly can be attributed to the lowered caloric intake, although obviously this is not the only factor involved.

The rats were killed after 130 days on the experimental diet. The average hemoglobin content of 4 rats was 93 per cent. The blood was pooled and the following determinations made: calcium 12.0, phosphorus 7.5, non-protein nitrogen 65, sugar 103 milligrams per cent.

Pathological findings

Technique. The animals were killed by etherization in the usual manner. The principal organs were immediately examined grossly and then fixed. Bouin's fluid and Zenker's fluid (Helly modification) were employed as fixatives. The tissues were then washed; dehydrated by increasingly stronger solutions of alcohol; cleared; embedded in paraffin; sectioned, and stained with haematoxylin and eosin.

Findings. 1. Newfoundland Cod Liver Oil (2 animals sectioned).

Gross appearance. The organs seemed entirely normal to the naked eye.

Microscopic appearance.

Heart. The endocardium, epicardium and valves showed no changes. There were a few small areas in which the muscle fibres stained somewhat more deeply than elsewhere. In these areas the nuclei and striations were entirely

normal. No areas of round-cell infiltration, focal necroses, calcium deposit or any other abnormal changes were seen. Sections of the great vessels showed no fat or calcium.

Liver. There were infrequently scattered small fat droplets within the liver cells. Otherwise the organ appeared to be normal.

Spleen. The picture here was an entirely normal one; the Malpighian bodies well defined, the splenic pulp rather poor in cells.

Kidney. There were no scars. The glomeruli were normal, as were the tubules, which contained no casts, albumin or red blood cells.

2. Norwegian Cod Liver Oil (4 animals sectioned).

Gross appearance. No abnormal variations were visible in any of the organs.

Microscopic appearance.

Heart. The endocardium, epicardium and valves were entirely normal. A few myocardial fibres took a slightly deeper stain, but again this was not associated with any abnormality of the nuclei or striations. The great vessels also were normal.

Liver. The hepatic lobules and cells were well preserved. The latter contained no fat.

Spleen. The normal structure was present. There were no lesions.

Kidney. The glomeruli, tubules and pelvis showed no variations from the normal. No scars were present.

3. Lard (Control group—3 animals sectioned).

Gross appearance. These animals showed an increased amount of subcutaneous and retroperitoneal fat. The livers of all were somewhat larger than normal and presented to the naked eye evidence that they were infiltrated with fat.

Microscopic appearance.

Heart. The endocardium, epicardium, valves and great vessels were normal throughout. The myocardium once more showed a slight staining irregularity, again a sole finding, no other lesions being present.

Liver. The liver cells contained an abundance of fat in globules, and stained with Scharlach R. No necroses or other changes were seen.

Spleen. There were no lesions present.

Kidney. In two of the animals the whole structure was entirely normal; in the third there were a few small fresh scars, with concentration of glomeruli, some of which showed adhesions. The associated tubules were moderately collapsed and contained albumin and casts in small amounts. The number of cells in the interstitial tissue was increased, these being all mononuclears.

Conclusions. The above results fail to confirm the effects described on various organs by previous authors, particularly by Agduhr. The constant presence of slight degrees of irregularity in the staining of the myocardium, as pronounced in the control as in the two experimental groups, seems almost surely an artefact. It may have been due to an unequal contraction of the fibres at the time of death; possibly also to minimal local disturbances in fixation. Being unassociated with any other demonstrable changes, it is hard to attach any importance to it. The presence of a low-grade nephritis in one of the control animals seems to be non-specific and merely a chance finding. It should be noted that only those organs in which the greatest pathological changes had been reported to occur were examined.

DISCUSSION

For some unexplained reason cod liver oil cannot be fed at high levels without deleterious effects. *The present paper does not detract from such a position;* it is to be regretted that no obvious explanation for this is forthcoming. The fact that *vitamin increases* in experimental diets can overcome the unfavorable influence of the oil is illuminating but not completely adequate. The presence of toxic amines in the oil prepared from fish livers would be a reasonable explanation were it not for the fact that present day medicinal cod liver oils have not been shown to contain such products (17, and unpublished results). The older method of preparing the oil, *i.e.*, allowing the livers to rot in the heat of the sun, and skimming off the oil as it rose to the top, undoubtedly gave rise to products of tissue

decomposition, but such conditions are not present in modern steam-rendering plants where the livers are rendered as soon as they are removed from the fish. A further line of fruitful investigation would be the pharmacological effects of small amounts of the highly unsaturated fatty acids characteristic of cod liver oil.

It is impossible to completely evaluate the work of Agduhr and his associates. His findings are rendered doubtful by (1) the lack of any pathological heart lesion, as reported in this paper, after feeding 60 times the dosage of cod liver oil that he used; (2) the fact that no other investigator has been able to confirm unequivocally Agduhr's results when "complete" diets were used; and (3) the further negative evidence that no such lesions have been reported (excepting Malmberg's findings—work done in Agduhr's laboratory) in the many children who have been fed 2 to 3 teaspoonfuls of cod liver oil from infancy onwards, when, for some other reason, they appeared at autopsy. We are inclined to believe that the explanation of Agduhr's results is to be found either in (a) the interpretation of his histological sections, (b) a deficiency of some accessory food constituent, or (c) the presence in his soil of some unknown substance which has not yet been proved to have a specific action on heart muscle, *e.g.*, certain toxic amines.

SUMMARY

1. No histological evidence of any pathological lesion was found in the hearts of rats fed for 130 days on a diet adequate in protein, salts and vitamins, but containing 78 per cent of the calories as cod liver oil.

2. The rate of growth of rats so fed was definitely subnormal. Several possible explanations of this fact are discussed.

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THE OCCURRENCE OF CYCLIC VARIATIONS IN MOTOR ACTIVITY IN RELATION TO THE MENSTRUAL CYCLE IN THE HUMAN FEMALE

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During recent years it has been established that in the laboratory animal there exist rhythmic changes in the "running" activity which can be correlated with certain phases of the oestrus cycle. Fluctuations in some of the physiological phenomena of the human have been carefully studied and reported by many, but relatively little attention has been paid to the possible occurrence of cyclic variations in the spontaneous motor activity of man. This has been due chiefly to the difficulty of measuring and controlling such activity.

A search of the literature has revealed no reference to studies of the motor activity of the human. The nearest approach to this is to be found in the study made by Dr. Carl G. Hartman (1) on one monkey in 1928 to 1930. Hartman demonstrated (fig. A) very definite cyclic variations in the activity of that monkey. There was a distinct rise in the activity curve at or just following each menstrual period. Following each peak, the activity curve gradually declined as the succeeding period was approached. He offers for consideration the possible relationship of motor-activity with the amount of oestrogenic substance contained in the blood. The studies and results herein reported would seem to indicate that a like phenomenon occurs in women.

The purpose of this paper is twofold: (1) to describe a method of procedure for the quantitative study of motor activity in the human; (2) to present what appears to be a cyclic variation of that activity in relation to the menstrual cycle and the accompanying changes in the amount of oestrogenic hormone in the blood of the human female.

The demands and customs of society, the drives and habits of the

individual, and the subject's reaction to wearing the required apparatus, all have to be considered in the evaluation of such activity data. Therefore, in every-day life it is exceedingly difficult to discriminate

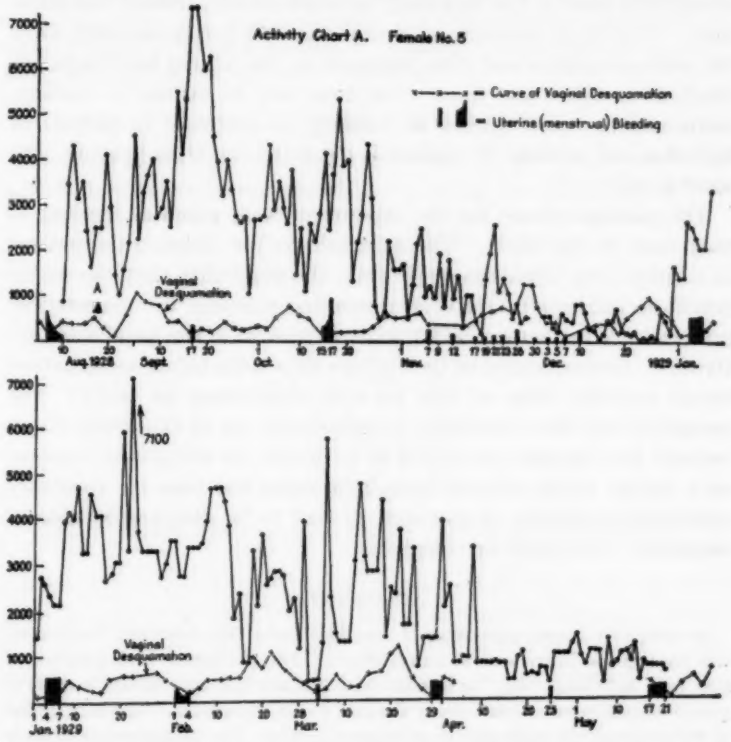

FIG. A. Reproduction from C. G. Hartman's "Studies on the Reproduction of the Monkey Macacus Rhesus, with special reference to menstruation and pregnancy." Spontaneous activity of female monkey in relation to the menstrual cycle. Bleedings are indicated by black areas, height roughly proportionate to abundance of flow.

between the necessary and the spontaneous activity of man because of the existence of many complicating factors. The closed, neutral and carefully controlled environment of the Henry Phipps Psychiatric

Clinic was chosen as the most convenient habitat in which to control these various factors. In the clinic the routine of living established for the patients consists of certain activities and duties which are maintained with more or less regularity as to occurrence, amount and duration. There is an adequate amount of time left during each day, after the various routines and clinic demands on the patient have been fulfilled, to be called free time. This time may be utilized in reading, conversation, indoor games or walking, as desired. In periods of agitation and tension the patient is not restricted from "pacing" the ward at will.

The patients chosen for the experiment were taken at random as they came to the clinic. The chief criteria for choosing the patient as a subject on admission were: first, the possibility that she would remain in the hospital for several months; secondly, her cooperativeness and thirdly, her capability to enter into all of the usual ward activities. Consequently, of the activity data collected on some sixteen female patients, those of only six were satisfactory for study. The remaining ten were considered unsuitable for use in this study either because they became too ill, had to be placed, for therapeutic reasons, on a regime which allowed them little or no free time for voluntary spontaneous activity of any sort, or had to be discharged before a menstrual cycle could be completed.

APPARATUS

A commonly known pedometer of American make (the American Pedometer) was used as the instrument of measurement. The pedometer is so constructed that with each body "jog," as in walking, a tumbler falls and through a series of geared wheels moves a hand about the face of the instrument. The face or dial of the pedometer is calibrated in quarters of a mile. The instrument is so made that the distance through which the tumbler falls can be gauged to the length of pace of the respective wearer. The instruments were worn inconspicuously attached to the clothing of the patients. Care was taken to attach the pedometers at the same body level in each case—namely, over the right anterior abdomen at hip level. The instruments were given the patients on their arising at 7 A.M. and were collected by the nursing staff when the patients retired for the night. The instruments were read daily and the records inserted under the corresponding patient's name and date of reading. They were all labeled with the patient's name, and care was taken to ensure that each individual wore the same instrument throughout the experiment.

Although the instruments were set to the pace of the persons wearing them, it soon became evident, on checking, that the number of miles registered by the instrument did not correspond exactly with the number of miles walked by the patient. However, if we assume that the instrument registers a certain proportional amount of movement, then the records should be considered as supplying an index to changes in the total body movement. The finer motor movements such as tremors, picking at the skin, rubbing of the hands, restless turning in the chair, variations in muscle tone, *etc.*, are not registered.

METHOD OF HORMONE DETERMINATION

The amount of the oestrogenic substance in the blood was determined approximately once weekly—by using the biological test as

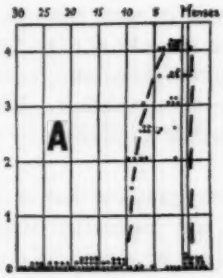

FIG. B. Reproduction from R. T. Frank's "The Female Sex Hormone"

described by Frank (2). This test, in brief, consists of extracting from 40 cc. of venous blood of the patient the oestrogenic substance which in turn is injected into a spayed and controlled white mouse. The cellular changes of the mouse's vaginal mucosa are assumed to indicate the amount of the substance injected. This test, to quote Frank (3), "is a qualitative method employed to obtain quantitative results." It, however, is the best method at hand for determining the relative amount of the "female sex hormone" in the blood and therefore the one of choice.

Frank (4) demonstrated (fig. B) that normally there is a premenstrual increase in the oestrogenic substance in the blood, followed by a rapid disappearance of it during, or immediately after, the menstrual flow.

RESULTS

Figure C. This chart shows the activity, as recorded by the pedometer, in each of five cases. It shows in every instance a definite post-menstrual increase in spontaneous gross body activity which gradually decreases as the succeeding menstrual period is approached.

The graphs were so drawn as to represent each actual pedometer reading in "miles" on the ordinates. The spaces representing the intra- and the inter-menstrual periods were fixed on the abscissae. These were divided, in each case, into the number of days of the menstrual flow in the former and the number of days between the periods of flow in the latter. Thus, there is no distortion in the actual curves —but they are compressed in some cases in order to make the menstrual periods coincide for the sake of easy comparison. The period of time included by the dotted lines and indicated by the letter "M" represents the period of menstrual flow. The number of days of the inter-menstruum in each case is indicated by the enumeration between the menstrual periods.

Patient 1. This activity graph is that of a 33-year-old woman who had never experienced any menstrual irregularity or dysfunction. She came to the hospital during a period of depression. She was somewhat tense and agitated, but on the whole was always capable of showing spontaneous interest in work and of carrying on all ward activities. The daily activity, except on the last one to three days of the menstrual flow and the first five to six days following the flow, averages approximately half a mile. This activity represents, at least, the amount necessary to follow out the ward routine. During the latter half of each period of menstrual flow the activity curve begins to rise. In the first inter-menstrual period the activity reaches a peak on the first and again on the fourth day. Following the second menstruation, peaks are noted on the second and fifth days. The second peak is higher than the first in each instance. The two post-menstrual curves are so strikingly alike in time, occurrence and form, that it is unlikely that this is a coincidence.

The hormone content of the blood of this patient was determined through one menstrual cycle and found to vary in amount as it did in Frank's 66 "normal women." In other words, the amount of oestro-

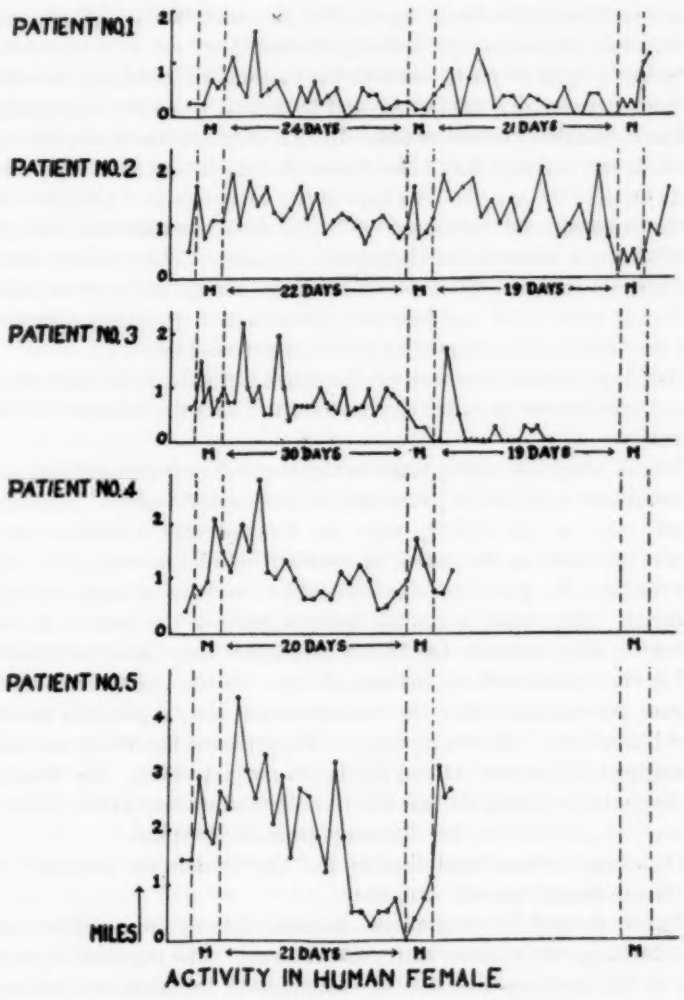

FIG. C. Spontaneous activity in the human female in relation to menstruation—five cases. "Pedometer miles" are indicated on the ordinates. Periods of bleeding are indicated by "M" and time in days on the abscissa.

genic substance in the blood was 0 when the activity was highest, and increased in amount as the activity decreased.

Patient 2, aged 30 years, came to the hospital for assistance in solving some personality difficulties and is normal in so far as activity and menstruation are concerned. In this graph there are no abrupt peaks in the activity curve like those in the first record. The two peaks on the 11th and the 17th days of the second cycle of this case are not to be considered "spontaneous." On these days she was advised to take active exercise for therapeutic reasons. Disregarding these two irregularities, it is then evident that the abrupt and quite definite rise in the curve at or just following menstruation gradually regresses to a low level as the succeeding period is approached.

The blood, in this case, was not examined for oestrogenic substance. Since she menstruated regularly, it is assumed that the hormone varied normally.

Patient 3, aged 30 years, came to the hospital so depressed that she was unable to fulfill the requirements of the hospital regime. The first twenty days of the activity data are therefore not described here. As she improved to the extent of showing interest in work, etc., she was considered a good experimental subject and her activity charted as shown. Here again are noted isolated peaks in the curve. In the first cycle they occur on the fourth and tenth days postmenstrually and in the second cycle on the second day. In the second inter-menstruum the plateau, after the postmenstrual rise, is partially on the base line of zero. However, despite this apparent inactivity she did, throughout this period, attend all classes and activities. She was exceedingly tense during the last fourteen days of her stay in the clinic—a result of anticipating her discharge from the hospital.

There was no menstrual disorder and the "female sex hormone" in the blood showed normal variations.

Patient 4, aged 19, entered the hospital directly from college and was discharged to re-enter active life at home. The psychiatric problem in this instance was that of vagueness in thinking and tension, with a sense of vaginal pulsations occurring in a setting of sexual preoccupation. She experienced no menstrual disorder. Here again one may note that the activity curve rises very perceptibly between the middle of the period of menstrual flow and the fourth day of the intermenstruum.

Patient 5. This record is that of a 16-year-old schizophrenic girl whose activity has been studied for nearly nine months. Her activity during the preceding one month and the succeeding seven months, although throughout definitely varying as herein shown, has not been incorporated in the graph. This was done because she was incapable of carrying on in a normal fashion on any of the active wards during that time.

This graph shows, more distinctly than any of the above, the post-menstrual activity rise followed by a gradual regression of the curve to the fourteenth day. At this time, the approximate date of ovulation, a sharp drop in activity occurs.

Blood hormone estimations, done weekly, revealed a gradually increasing amount of the oestrogenic substance from the sixteenth day to the middle of the next menstrual period. At the middle of this menstrual period, it rapidly decreased as in the preceding cases.

Thus it is possible to say that with the abrupt fall in the blood hormone, at or immediately after menstruation, there is a corresponding sudden burst of activity.

It is also worthy of mention that the behavior charts made daily by the nursing staff on each patient show objectively an occurrence of an increase in irritability, restlessness, disinterest, and mood disturbances; and a decrease in spontaneity during the seven to twelve days preceding each menstrual period. Subjectively, during this period of time, several of the patients complained of various genital, breast and leg sensations, of being "tense," of head pressures, of sex dreams and preoccupations, of a lowering of mood, of broken sleep, and of "feeling worse in general." Further mention of these phenomena will be made in the discussion to follow.

Figure D. The findings in Case 6, represented in figure D, are reported apart from the first 5 cases because this patient was not only amenorrheic for a considerable period of time, but also presented some very striking psychobiological disturbances in the form of stupor, behavior and content. These appeared to be definitely related to the oestrogenic-substance content of the blood and the motor activity. In this case the activity was recorded and charted as in the cases shown in figure A. The amount of this hormone in the blood is represented by the lower graph of figure D. On the abscissae time is represented

in days to correspond chronologically with the activity curve of the same graph. The oestrogenic substance in 40 cc. of blood was determined by the method described by Frank (3) and plotted on the ordinate. A vaginal secretion in which leucocytes and mucus only are present is considered a 0 reaction and indicates an absence of any "female sex hormone"; a 1 and 2 reaction, as evidenced by an influx of proportional numbers of epithelial cells in the secretion, a possible

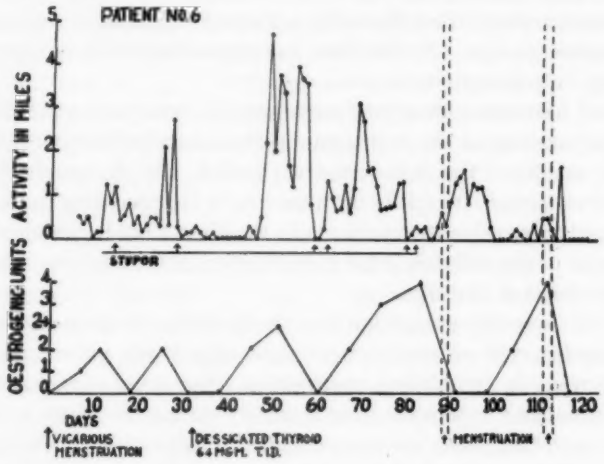

FIG. D. Upper graph represents activity in miles indicated on the ordinate. Time in days indicated on the abscissa. Lower graph represents the amount of oestrogenic substance in the blood indicated on the ordinate. Time in days indicated as in upper graph.

presence of the hormone; a 2+, a definite presence of the substance; a 3 reaction, more substance present; and a 4 reaction, a very positive test. A 4 reaction is represented by the production of the complete cornification of the epithelial cells of the vaginal secretion of the test animal, and is the same as found in the intact animal at oestrus.

The case is that of a 20-year-old unmarried girl who menstruated regularly without difficulty from 13 to 16 years of age. At the latter age, on intimate association with young men, she experienced numbness of the legs and since then has had somewhat irregularly occurring

menses, with considerable dysmenorrhea. When 18 years old—in February, 1930—she had epistaxis with a menstrual period. In June, 1930, in a setting of a schizophrenic upheaval, she developed marked low-back pain, numbness of the legs, and menstruated scantily on two occasions at an interval of seven days. Menses came again regularly until finally, in August 1932, a menstrual flow occurred while she was in a profound stupor of five days' duration. Following this, amenorrhea was present for five months. Then (January 1933), for the last time before her admission to the hospital, menstruation again came on during a stupor lasting ten days. Since then the clinical picture has been one of most odd, incongruous and queer behavior and content. She entered H.P.P.C. on June 11, 1933. Several days later she had a severe epistaxis associated with abdominal cramps (no vaginal bleeding). This was thought to be a vicarious menstruation. On this date the present activity record and blood hormone studies were begun.

The activity record (*figure D*). It is clearly discernible that there are 6 major activity peaks and that menstruation came on just before each of the two last peaks, or on the 93rd and 115th days. Preceding the first regular menstruation, on the 93rd day, there occurred, following each of the first two activity peaks, a stupor lasting from one hour to twelve hours. The first burst of activity followed by stupor occurred 14 days after the vicarious menstruation (approximate time of ovulation). The second burst, with stupor following, occurred 22 days after the vicarious bleeding,—a period of time equal to the last intermenstrual period plotted. The third rise in activity occurred 27 days after the second—again at about the calculated intermenstrual period. The fourth activity peak occurred 21 days after the third and 23 days before the fifth. Midway between the third and fourth and the fourth and fifth peaks stupor occurred. If, since the last two activity peaks occurred just postmenstrually (as was noted in the more normal group of cases presented in graph A), one can assume, because of the time allocation, that each of the preceding activity bursts was associated in some way with endocrine function, probably ovarian activity; again reasoning from the chronology of these phenomena, one would be led to believe that the stupors were present at about the time ovulation should have occurred, except in the instance of the second which

occurred some 28 days after the vicarious bleeding. No stupors occurred after the menstruation was reëstablished.

The hormone graph—figure D. The blood was tested at approximately weekly intervals for the amount of contained oestrogenic substance. The results of these tests are graphed on the lower half of figure D. A very slight amount was present at the time of the first two activity curve peaks and succeeding stupor reactions. On the 32nd day of the experiment desiccated thyroid extract (64 mgm. t.i.d.) was begun because the patient's BMR was found to be −23 per cent. Thereafter it is very interesting to note that both the activity and amount of female sex hormone in the blood increased. It is also to be noted that the activity curve as well as that of the hormone began to assume the normal curves. Sixty days after thyroid therapy had been begun, two normal menses were experienced with corresponding normal fluctuations in the amount of blood hormone and motor activity.

From this study the following is evident: (1) that the hormone and activity data revealed a time relationship of the stupors synchronous with phases of the menstrual cycle; (2) that there is suggested a correlation between the degree of motor activity and the amount of the oestrogenic substance in the blood; (3) that without overt signs of menstruation, there were existent certain fairly regular ovarian function cycles. And (4) these cycles were made more regular, more pronounced and gradually returned more nearly to normal following the administration of thyroid extract.

DISCUSSION

The foregoing data demonstrate that there is some relationship between the human female's muscular activity and the amount of the oestrogenic substance in her blood—*viz.*, a postmenstrual increase in activity which gradually regresses to a low level just preceding the next period. The question immediately arises: How this can be explained?

As early as 1876, Mary Jacobi (6) expressed the opinion that physical and possibly mental activities may fluctuate in relation to the menstrual cycle.

From the work of Kind, V. Ott, Van de Veldt, Reinle and others

there seems to be an indication that in the woman there occurs a gradual premenstrual rise and an abrupt postmenstrual drop in pulse rate, blood pressure, pulmonary capacity, heat radiation, body temperature, muscular power, and reflex excitability.

Wang (7), *in a study of the rat*, demonstrated that "the activity cycle bears an intimate time relation to the oestrous rhythm, the female rat being most active in the period of oestrus." In other words, the female rat does more "running" when her oestrogenic substance content is greatest in amount. Richter (8) has recently shown that the total activity of the spayed, and to some extent of the normal female rat, can be considerably increased by the injection of Amniotin (Squibb and Co.).

With the exception of Hartman's findings on the activity of the monkey, the experimental work on rats and the afore-mentioned physiological and metabolic studies on the human would lead one to expect the activity curve of the human female to be quite the reverse of that actually demonstrated in this study. One could well imagine that were it possible to measure and record all of the activity—such as increase in muscle tone, restlessness, agitation, etc.—the resulting data, if recorded in graph form, would likely be in accord with the physiological fluctuations of blood pressure, temperature, etc., mentioned above. However, in a study of spontaneous, constructive activity, agitation, restlessness and tension are not objectively to be determined. It is the opinion of the author that with and following menstruation there is a subjective decrease in tension and a resultant feeling of ease and freedom. With this freedom the individual feels more inclined to constructive spontaneous action, and apparently does act more in this manner. This surmise is supported by a comparable phenomenon in the rat. Kinder (8) (as shown in figure E) stated, "The nest building of the adult rat shows cyclic variations synchronous with the oestrous cycle, the maximum of nest building occurring during the dioestrous interval and the minimum at the time of oestrus. The cycle of nest-building activity is thus the reverse of the running activity found by Wang and Slonaker." It would seem to me that the running record of the rats which Wang reported are composed not only of spontaneous activity but very likely of movements resulting from tension and restlessness. The nest building is a voluntary, spontaneous and constructive type of activity.

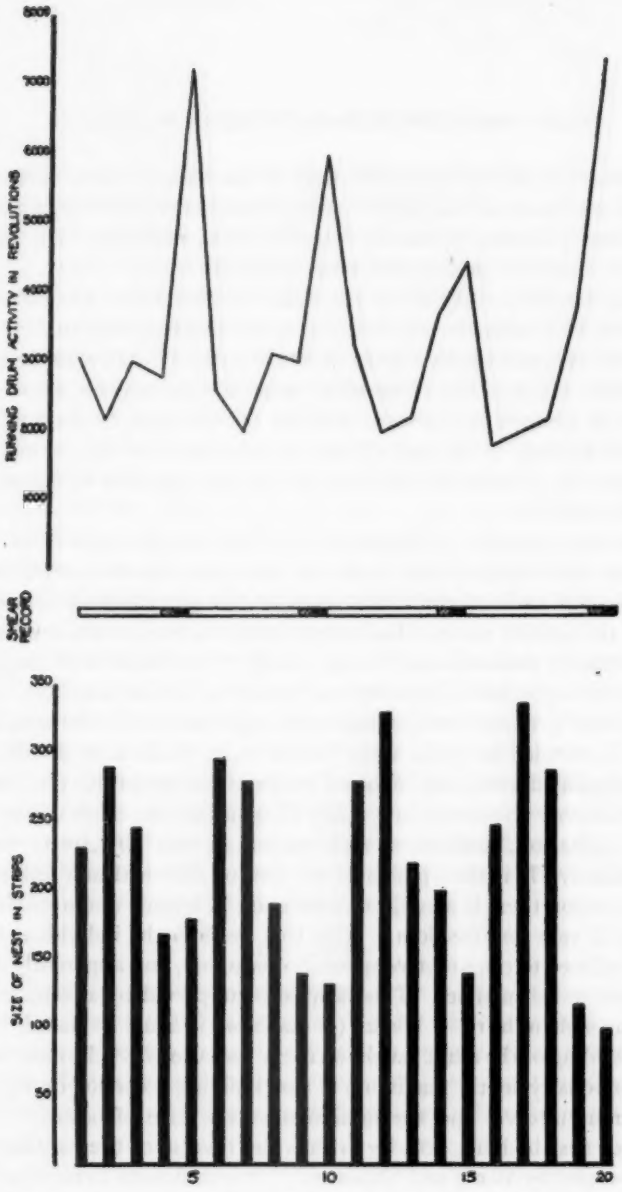

FIG. E. Reproduction from Elaine F. Kinder's "A Study of the Nest-Building Activity of the Albino Rat." *Jour. Exp. Zool.*, **47**, 2, April 1927. A composite nest-building curve giving averages for 3 animals, litter mates, for successive days during four ovulation cycles. Smear findings are given between the graphs. Ordinates; size of nest in strips of nesting material. Abscissae; successive days of the experiment.

In the remarks regarding the cases presented in figure C, mention was made of the premenstrual subjective tension sensations. It is a view of Dr. Adolf Meyer that there might be some connection between such tension feelings and smooth muscle spasm in the region of the sensation. Hisaw (9) and others are of the opinion that, experimentally, the oestrogenic substance does stimulate smooth musculature to contraction. Since it is during the few days preceding menstruation that the oestrogenic substance is to be found in highest concentration in the blood, it is suggested that the feeling of "tightness," tingling and the other so-called tension sensations, common to that period, are perhaps in part associated with an increase in smooth muscle tone due to stimulation by this substance.

In *summary*, it is hoped that this simple and preliminary report may be of some value in that it suggests whereby the spontaneous activity of the woman, in relation to the menstrual cycle, can be better understood. There is a definite and increasing need in medicine to recognize, understand, and treat an individual as an integrated organism and not just merely as a series of systems or functioning parts. To supply this need a more thorough study of the endocrinological and activity function and their occurrence in, and relationship to, the total personality is necessary.

CONCLUSIONS

1. A method of recording human activity is described.
2. The activity graphs of all six cases reported show a consistent postmenstrual burst of activity which gradually declines to the time of the succeeding menstrual period.
3. A theory is advanced that the subjective tension symptoms common to the premenstruum may be due to hormonal stimulation of the smooth musculature.
4. A case of amenorrhea is presented in which there is demonstrated a definite relationship of activity, the amount of oestrogenic substance in the blood, menstruation and behavior; and how all were affected by the administration of thyroid extract.
5. The necessity for more study of the endocrine functions and activity in their relations to the total personality is pointed out.

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BOOK REVIEWS

The Thyroid Gland. Its Chemistry and Physiology. By CHARLES ROBERT HARINGTON. 235 pp. $4.50. (*Oxford Univ. Press, N. Y., 1933.*)

This book deals with the biochemistry of thyroid secretion, hyperthyroidism and hypothyroidism. The brief historic introduction is excellent, and the critical survey of such phases as goitre and cretinism, thyroxine and the biochemical aspects of Graves' disease is exhaustive and authoritative.

L. H.

Diseases of the Nervous System. By W. RUSSELL BRAIN. 899 pp. $8.75. (*Oxford Univ. Press, N. Y., 1933.*)

Beginning with a concise exposition of neuro-anatomy and neurophysiology, this volume covers the known nervous diseases, including chapters on extra-pyramidal syndromes, disorders of the peripheral nerves and the autonomic system, winding up with a discussion of nervous disorders in relation to life insurance. The terminal list of references is well chosen. The language is clear and to the point, and little space is given to conflicting theories of causation. For the student and clinician this is probably the best presentation of clinical neurology that has yet appeared.

W. C.

The Anatomy of the Eye and Orbit. By EUGENE WOLFF. 1933. 310 pp. Illust. $7.50. (*P. Blakiston's Son & Co., Inc., Phila.*)

This book is unsurpassed for its interesting, clear, vivid presentation of anatomical facts. The numerous clinical references are especially valuable and the illustrations are exceptionally well done.

T. O. C.

Nosography. The Evolution of Clinical Medicine in Modern Times. By KNUD FABER. 2nd edit. Pp. 222. (*Paul B. Hoeber Inc., N. Y., 1930.*)

In a day when laboratory science is so firmly seated in the saddle, it is stimulating to read of the rôle that the analytical mind of the clinician has played in the advance of medical knowledge. Dr. Faber, Professor of Internal Medicine at Copenhagen, has written the next best book after Petersen's [now unobtainable] on the elucidation of the great problems of disease. Already in a first edition and well-known, it is now expanded in a second edition. This provocative and scholarly brochure is welcomed heartily by all those who are interested in the development, since the time of Sydenham, of observation and influence at the bedside.

C. A. J.

The Joy of Living. An Autobiography. By FRANKLIN H. MARTIN. 2 vols. Vol. 1: Personal & Professional Reminiscences. 491 pp. Vol. 2: The World War. 526 pp. $10.00 set. (*Doubleday, Doran & Co., Inc., N. Y. 1933.*)

Among civilians who took over the burdens of medical administration during the World War, there were none more prominent and efficient than Dr. Franklin H. Martin. In many difficult situations, he was a tower of strength. These volumes record the activities, as well as details of his early life. The illustrations alone are a valuable record of the war period in Washington.

R. L. M.

Gastric Anacidity. Its Relation to Disease. By ARTHUR L. BLOOMFIELD and W. SCOTT POLLARD. 188 pp. $2.50. (*Macmillan Co., New York, 1933.*)

In this very readable volume, the authors have reviewed the available literature pertaining to incidence, age at onset, etiology, pathological findings, clinical associations, prognosis and treatment of gastric anacidity. As a great deal of their own excellent work is included, the book is made the more authoritative. Among the many noteworthy features is their review of old literature and their careful sifting of the wheat from the chaff. For, as they show, a great deal of misinformation, the only criterion of which is its hoary age, has been passed on from year to year.

The description of the chemistry of the gastric juice lacking in hydrochloric acid, and the demonstration of the practical significance of hydrogen-ion determinations in questionable cases, are to the point and well done. Another important point is their summation of data on the blood in cases of anacidity, especially in the so-called "achylic hypochromic anemia" which they believe is not a specific disease. They show that the great majority of achylic women are not anemic and that many women may be anemic without an associated anacidity.

Full summaries of the work on the association of anacidity with pernicious anemia and with gastric neoplasms are included. The pathological data on anemia are particularly good. The authors make the very sensible point that gastric anacidity is not necessarily the primary event in pernicious anemia but that it plays at least an important part in promoting the anemia. They believe that "the true explanation of the complex relationship between the anacidity, the anemia, the cord changes and other features has not yet been finally settled."

Valuable and detailed data on the association of anacidity and many disease conditions—fevers, acute and chronic, endocrine disorders, etc.,—are given for easy reference.

As to secretion of pepsin in anacidity our authors find it in normal concentration but in relatively small amount due to the paucity of gastric secretion. They also state that "acid and ferment fail hand in hand; in all instances of *true anacidity* secretion is reduced to a negligible minimum." It would seem more satisfactory if their first analysis were allowed to have sway, for the important point is made that pepsin (even though in small quantity) is secreted in the absence of hydrochloric acid.

The book is well-written, the statements are conservative and there is a great deal of new and original thought. It well deserves the examination of all students of medicine.

L. M.

Mayou's Diseases of the Eye. By FREDERICK RIDLEY and ARNOLD SORSBY. 4th Edition. 249 pp. $2.25. (*Oxford Univ. Press, New York, 1933.*)

This excellent little handbook for the use of medical students has been thoroughly revised and brought up to date. Though only an outline of ophthalmology, it covers the field very well and forms an excellent introduction to the subject. The illustrations are few but well chosen.

B. R.

Bentley and Driver's Textbook of Pharmaceutical Chemistry. By JOHN EDMUND DRIVER. 2nd ed. 538 pp. (*Oxford Univ. Press, New York, 1933.*)

A worthwhile textbook of pharmaceutical chemistry for students who have had an introductory course in general chemistry. Unfortunately for American students, the terminology and analytical procedures are based on the British Pharmacopoeia.

J. F. S., JR.

PROGRAMS AND LECTURES, 1933–1934

Programs of The Johns Hopkins Medical Society

November 13, 1933

Forced Drainage of Cerebro-spinal Fluid in the Treatment of Infectious Diseases of the Central Nervous System. Lawrence S. Kubie, M.D., New York.

Classification and Treatment of Anaemia on the Basis of Difference in the Size of Hemoglobin Contents of the Red Blood Corpuscles. M. M. Wintrobe, M.D.

December 11, 1933

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Glomerular Changes in Nephritis. W. G. MacCallum, M.D.

Experimental Exophthalmos and Hyperthyroidism. Harry B. Friedgood, M.D.

January 8, 1934

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Hematoporphuria. Harriet Guild, M.D.

Preoperative Radiation of Malignant Tumors of the Kidney. Lawrence Wharton, M.D.

February 12, 1934

Living Grafts of Endocrine Glands. Harvey B. Stone, M.D., James D. Owings, M.D., and George O. Gey, M.D.

Influence of Plasma and Plasma Extract on Haemolytic Anaemia. Hugh Josephs, M.D.

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The Action of Some Ergot Preparations on the Human Uterus. A. K. Koff, M.D.

The Epidemiology of Diphtheria. Wade H. Frost, M.D.

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A Summary of our Present Knowledge Concerning Minute Hemolytic Streptococci. Perrin H. Long, M.D., Eleanor A. Bliss, S.D., and Charles I. Walcott, M.D.

Studies Upon the Mechanism of Hyperthyroidism: A. Alterations in Tissue Respiration. B. Alterations in Lactic Acid Metabolism. Donald McEachern, M.D., and E. Cowles Andrus, M.D.

May 14, 1934

Primary Tumor of the Ureter, Report of Case, with a New Technique for Complete Nephroureterectomy. J. A. C. COLSTON, M.D.
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In Celebration of the Eightieth Birthday of Dr. Karl Sudhoff, Professor-Emeritus of the History of Medicine at the University of Leipzig
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Karl Sudhoff as Editor and Bibliographer. FIELDING H. GARRISON, M.D.
Karl Sudhoff the Classical Philologian. JOHN RATHBONE OLIVER, M.D.
Sudhoff the Rediscoverer of Paracelsus. OWSEI TEMKIN, M.D.
Karl Sudhoff the Mediaevalist. HENRY E. SIGERIST, M.D.

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April 12, 1934

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May 17, 1934

The Syphilis of Fracastoro with Some Observations on the Origin and History of the Word Syphilis. GEORGE L. HENDRICKSON, M.D., Yale University.
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